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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of: Yue et al.

Title: INTRACELLULAR SIGNALING MOLECULES

Serial No.: 10/018,170 Filing Date: December 11, 2001

Examiner: Steadman, D Group Art Unit: 1652

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**DECLARATION OF DR. TOD BEDILION**  
**UNDER 37 C.F.R. § 1.132**

I, TOD BEDILION, a citizen of the United States, residing at 132 Winding Way, San Carlos, California, declare that:

1. I was employed by Incyte Genomics, Inc. (hereinafter "Incyte") as a Director of Corporate Development until May 11, 2001. I am currently under contract to be a Consultant to Incyte Genomics, Inc.

2. In 1996, I received a Ph.D. degree in Cell, Molecular and Development Biology from UCLA. I had previously received, in 1988, a B.S. degree in biology from UCLA.

Upon my graduation from UCLA, I became, in April 1996, the first employee of Synteni, Inc. (hereinafter "Synteni"). I was a Research Director at Synteni from April 1996 until Synteni was acquired by Incyte in early 1998.

I understand that Synteni was founded in 1994 by T. Dari Shalon while he was a graduate student at Stanford University. I further understand that Synteni was founded for the purpose

of commercially exploiting certain "cDNA microarray" technology that was being worked on at Stanford in the early to mid-1990s. That technology, which I will sometimes refer to herein as the "Stanford-developed cDNA microarray technology", was the subject of Dr. Shalon's doctoral thesis at Stanford. I understand and believe that Dr. P.O. Brown was Dr. Shalon's thesis advisor at Stanford.

During the period beginning before I was employed by Synteni and ending upon its acquisition by Incyte in early 1998, I understand Synteni was the exclusive licensee of the Stanford-developed cDNA microarray technology, subject to any right that the United States government may have with respect to that technology. In early 1998, I understand Incyte acquired rights under the Stanford-developed cDNA microarray technology as part of its acquisition of Synteni.

I understand that at the time of the commencement of my employment at Synteni in April 1996, Synteni's rights with respect to the Stanford-developed cDNA technology included rights under a United States patent application that had been filed June 7, 1995 in the names of Drs. Brown and Shalon and that subsequently issued as United States Patent No. 5,807,522 (the Brown '522 patent). In December 1995, the subject matter of the Brown '522 patent was published based on a PCT patent application that had also been filed in June 1995. The Brown '522 patent (and its corresponding PCT application) describes the use of the Stanford-developed cDNA technology in a number of gene expression monitoring applications, as will be discussed more fully below.

Upon Incyte's acquisition of Synteni, I became employed by Incyte. From early 1998 until late 1999, I was an Associate Research Director at Incyte. In late 1999, I was promoted to the position of Director, Corporate Development.

I have been aware of the Stanford-developed cDNA microarray technology since shortly before I commenced my employment at Synteni. While I was employed by Synteni, virtually all (if not all) of my work efforts (as well as the work efforts of others employed by Synteni) were directed to the further development and commercial exploitation of that cDNA microarray technology. By the end of 1997, those efforts had progressed to the point that I understand Incyte agreed to pay at least about \$80 million to acquire Synteni. Since I have been employed by Incyte, I have continued to work

on the further development and commercial exploitation of the cDNA microarray technology that was first developed at Stanford in the early to mid-1990s.

3. I have reviewed the specification of a United States patent application that I understand was filed on December 11, 2001 in the names of Yue et al. and was assigned Serial No. 10/018,170 (hereinafter “the Yue ‘170 application”). Furthermore, I understand that this United States patent application claimed priority to United States Provisional Patent Application Serial No. 60/139,566 filed on June 16, 1999 (hereinafter “the Yue ‘566 application”). The SEQ ID NO:12-encoding polynucleotides were described in the Yue ‘566 application. (Note that the sequences of SEQ ID NO:12 and SEQ ID NO:64 disclosed in the Yue ‘170 application are identical to the sequences referred to as SEQ ID NO:12 and SEQ ID NO:31, respectively, in the Yue ‘566 application). My remarks herein will therefore be directed to the Yue ‘566 patent application, and June 16, 1999, as the relevant date of filing. In broad overview, the Yue ‘566 specification pertains to certain nucleotide and amino acid sequences and their use in a number of applications, including gene expression monitoring applications that are useful in connection with (a) developing drugs (e.g., the diagnosis of inherited and acquired genetic disorders, expression profiling, toxicology testing, and drug development with respect to cancer, an immunopathology, a neuropathology, and the like), and (b) monitoring the activity of drugs for purposes relating to evaluating their efficacy and toxicity.

4. I understand that (a) the Yue ‘566 application contains claims that are directed to isolated and purified polynucleotides having the sequences disclosed in the Yue ‘170 application as SEQ ID NO:12-encoding polynucleotides, for example SEQ ID NO:64 (hereinafter “the SEQ ID NO:12-encoding polynucleotides”), and (b) the Patent Examiner has rejected those claims on the grounds that the specification of the Yue ‘566 application does not disclose a substantial, specific and credible utility for the claimed SEQ ID NO:12-encoding polynucleotides. I further understand that whether or not a patent specification discloses a substantial, specific and credible utility for its claimed subject matter is properly determined from the perspective of a person skilled in the art to which the specification pertains at the time of the patent application was filed. In addition, I understand that a substantial, specific and credible utility under the patent laws must be a “real-world” utility.

5. I have been asked (a) to consider with a view to reaching a conclusion (or conclusions) as to whether or not I agree with the Patent Examiner's position that the Yue '566 application does not disclose a substantial, specific and credible "real-world" utility for the claimed SEQ ID NO:12-encoding polynucleotides, and (b) to state and explain the bases for any conclusions I reach. I have been informed that, in connection with my considerations, I should determine whether or not a person skilled in the art to which the Yue '566 application pertains on June 16, 1999 would have concluded that the Yue '566 application disclosed, for the benefit of the public, a specific beneficial use of the SEQ ID NO:12-encoding polynucleotides in their then available and disclosed form. I have also been informed that, with respect to the "real-world" utility requirement, the Patent and Trademark Office instructs its Patent Examiners in Section 2107 of the Manual of Patent Examining Procedure, under the heading "I. 'Real-World Value' Requirement":

"Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact 'useful' in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified utility and inventions whose specific utility requires further research to identify or reasonably confirm."

6. I have considered the matters set forth in paragraph 5 of this Declaration and have concluded that, contrary to the position I understand the Patent Examiner has taken, the specification of the Yue '566 patent application disclosed to a person skilled in the art at the time of its filing a number of substantial, specific and credible real-world utilities for the claimed SEQ ID NO:12-encoding polynucleotides. More specifically, persons skilled in the art on June 16, 1999 would have understood the Yue '566 application to disclose the use of the SEQ ID NO:12-encoding polynucleotides in a number of gene expression monitoring applications that were well-known at that time to be useful in connection with the development of drugs and the monitoring of the activity of such drugs. I explain the bases for reaching my conclusion in this regard in paragraphs 7-16 below.

7. In reaching the conclusion stated in paragraph 6 of this Declaration, I considered (a) the specification of the Yue '566 application, and (b) a number of published articles and patent documents that evidence gene expression monitoring techniques that were well-known before the June 16, 1999 filing date of the Yue '566 application. The published articles and patent documents I considered are:

- (a) Schena, M., Shalon, D., Heller, R., Chai, A., Brown, P.O., and Davis, R.W., Parallel human genome analysis: Microarray-based expression monitoring of 1000 genes, Proc. Natl. Acad. Sci. USA, 93, 10614-10619 (1996) (hereinafter "the Schena 1996 article") (copy annexed at Tab A);
- (b) Schena, M., Shalon, D., Davis, R.W., Brown, P.O., Quantitative Monitoring of Gene Expression Patterns with a Complementary DNA Microarray, Science, 270, 467-470 (1995) (hereinafter "the Schena 1995 article") (copy annexed at Tab B);
- (c) Shalon and Brown PCT patent application WO 95/35505 titled "Method and Apparatus For Fabricating Microarrays Of Biological Samples," filed on June 16, 1995, and published on December 28, 1995 (hereinafter "the Shalon PCT application") (copy annexed at Tab C);
- (d) Brown and Shalon U.S. Patent No. 5,807,522, corresponding to the Shalon PCT application, titled "Methods For Fabricating Microarrays Of Biological Samples," filed on June 7, 1995 and issued on September 15, 1998 (hereinafter "the Brown '522 patent") (copy annexed at Tab D);
- (e) DeRisi, J., Penland, L., and Brown, P.O. (Group 1); Bittner, M.L., Meltzer, P.S., Ray, M., Chen, Y., Su, Y.A., and Trent, J.M. (Group 2), Use of a cDNA microarray to analyse gene expression patterns in human cancer, Nat. Genet., 14(4), 457-460 (1996) (hereinafter "the DeRisi article") (copy annexed at Tab E);
- (f) Shalon, D., Smith, S.J., and Brown, P.O., A DNA Microarray System for Analyzing Complex DNA Samples Using Two-color Fluorescent Probe Hybridization, Genome Res., 6(7), 639-645 (1996) (hereinafter "the Shalon article") (copy annexed at Tab F);
- (g) Heller, R.A., Schena, M., Chai A., Shalon, D., Bedilion, T., Gilmore, J., Woolley, D.E., and Davis R.W., Discovery and analysis of inflammatory disease-related genes using

cDNA microarrays, Proc. Natl. Acad. Sci. USA, 94, 2150-2155 (1997) (hereinafter "the Heller article") (copy annexed at Tab G);

(h) Sambrook, J., Fritsch, E.F., Maniatis, T., Molecular Cloning, A Laboratory Manual, pages 7.37 and 7.38, Cold Spring Harbor Press (1989) (hereinafter "the Sambrook Manual") (copy annexed at Tab H);

8. Many of the published articles and patent documents I considered (i.e., at least items (a)-(g) identified in paragraph 7) relate to work done at Stanford University in the early and mid-1990s with respect to the development of cDNA microarrays for use in gene expression monitoring applications under which Synteni became exclusively licensed. As I will discuss, a person skilled in the art who read the Yue '566 application on June 16, 1999 would have understood that application to disclose the SEQ ID NO:12-encoding polynucleotides to be useful for a number of gene expression monitoring applications, e.g., as a probe for the expression of that specific polynucleotide in cDNA microarrays of the type first developed at Stanford.

9. Turning more specifically to the Yue '566 specification, the SEQ ID NO:64 polynucleotide (referred to as SEQ ID NO:31 in the Yue '566 application) is shown at p. 33 as one of 38 sequences under the heading "Sequence Listing." The Yue '566 specification specifically teaches that the invention provides isolated and purified polynucleotides that encode INSIG (Yue '566 application at p. 3). It further teaches that (a) the identity of the SEQ ID NO:64 polynucleotide was determined from a diseased gallbladder tissue cDNA library (GBLANOT01) (Yue '566 application, Table 4), (b) the SEQ ID NO:64 polynucleotide encodes for the annexin protein (INSIG) shown as SEQ ID NO:12 (Yue '566 application at Tables 1 and 2), and (c) northern analysis of SEQ ID NO:64 shows its expression predominantly in cDNA libraries associated with reproductive, gastrointestinal, and nervous system tissues and in tissues associated with cancer and inflammation (Yue '566 application at Table 4).

The Yue '566 application discusses a number of uses of the SEQ ID NO:12-encoding polynucleotides in addition to their use in gene expression monitoring applications. I have not fully evaluated these additional uses in connection with the preparation of this Declaration and do not express any views in this Declaration regarding whether or not the Yue '566 specification discloses

these additional uses to be substantial, specific and credible real-world utilities of the SEQ ID NO:12-encoding polynucleotides. Consequently, my discussion in this Declaration concerning the Yue '566 application focuses on the portions of the application that relate to the use of the SEQ ID NO:12-encoding polynucleotides in gene expression monitoring applications.

10. The Yue '566 application discloses that the polynucleotide sequences disclosed therein, including the SEQ ID NO:12-encoding polynucleotides, are useful as probes in microarrays. It further teaches that the microarrays can be used "to monitor the expression level of large numbers of genes simultaneously" for a number of purposes, including "to develop and monitor the activities of therapeutic agents" (Yue '566 application at p. 34, lines 10-15).

In the paragraph immediately following the Yue '566 teachings described in the preceding paragraph of this Declaration, the Yue '566 application teaches that microarrays can be prepared using the previously mentioned cDNA microarray technology developed at Stanford in the early to mid-1990s. In this connection, the Yue '566 application specifically cites to the Schena 1996 article identified in item (a) of paragraph 7 of this Declaration (Yue '566 application at p. 34; *supra*, paragraph 7).

The Schena 1996 article is one of a number of documents that were published prior to the June 16, 1999 filing date of the Yue '566 application that describes the use of the Stanford-developed cDNA technology in a wide range of gene expression monitoring applications, including monitoring and analyzing gene expression patterns in human cancer. In view of the Yue '566 application, the Schena 1996 article, and other related pre-June, 1999 publications, persons skilled in the art on June 16, 1999 clearly would have understood the Yue '566 application to disclose the SEQ ID NO:12-encoding polynucleotides to be useful in cDNA microarrays for the development of new drugs and monitoring the activities of drugs for such purposes as evaluating their efficacy and toxicity, as explained more fully in paragraph 15 below.

With specific reference to toxicity evaluations, those of skill in the art who were working on drug development in June, 1999 (and for many years prior to June, 1999) without any doubt appreciated that the toxicity (or lack of toxicity) of any proposed drug they were working on was one of the most important criteria to be considered and evaluated in connection with the development

of the drug. They would have understood at that time that good drugs are not only potent, they are specific. This means that they have strong effects on a specific biological target and minimal effects on all other biological targets. Ascertaining that a candidate drug affects its intended target, and identification of undesirable secondary effects (i.e., toxic side effects), had been for many years among the main challenges in developing new drugs. The ability to determine which genes are positively affected by a given drug, coupled with the ability to quickly and at the earliest time possible in the drug development process identify drugs that are likely to be toxic because of their undesirable secondary effects, have enormous value in improving the efficiency of the drug discovery process, and are an important and essential part of the development of any new drug. Accordingly, the teachings in the Yue '566 application, in particular regarding use of the SEQ ID NO:12-encoding polynucleotides in differential gene expression analysis and in the development and the monitoring of the activities of drugs, clearly includes toxicity studies and persons skilled in the art who read the Yue '566 application on June 16, 1999 would have understood that to be so.

11. The Schena 1996 article was not the first publication that described the use of the cDNA microarray technique developed at Stanford to monitor quantitatively gene expression patterns. More than a year earlier (i.e., in October 1995), the Schena 1995 article, titled "Quantitative Monitoring of Gene Expression Patterns with a Complementary DNA Microarray", was published (see Tabs A and B).

12. As previously discussed (*supra*, paragraphs 2 and 7), in the mid-1990s patent applications were filed in the names of Drs. Shalon and Brown that described the Stanford-developed cDNA microarray technology. The two patent documents (i.e., the Shalon PCT application and the Brown '522 patent) annexed to this Declaration at Tabs C and D evidence information that was available to the public regarding the Stanford-developed cDNA microarray technology before the June 16, 1999 filing date of the Yue '566 application.

The Shalon PCT patent application, which was published in December 1995, contains virtually the same (if not exactly the same) specification as the Brown '522 patent. Hence, the Brown '522 patent disclosure was, in effect, available to the public as of the December 1995 publication date

of the Shalon PCT application(see Tabs C and D). For the sake of convenience, I cite to and discuss the Brown '522 specification below on the understanding that the descriptions in that specification were published as of the December 28, 1995 publication date of the Shalon PCT application.

The Brown '522 patent discusses, in detail, the utility of the Stanford-developed cDNA microarrays in gene expression monitoring applications. For example, in the "Summary Of The Invention" section, the Brown '522 patent teaches (see Tab D, col. 4, line 52-col. 5, line 8):

Also forming part of the invention is a method of detecting differential expression of each of a plurality of genes in a first cell type, with respect to expression of the same genes in a second cell type. In practicing the method, there is first produced fluorescent-labeled cDNAs from mRNAs isolated from two cells types, where the cDNAs from the first and second cell types are labeled with first and second different fluorescent reporters.

A mixture of the labeled cDNAs from the two cell types is added to an array of polynucleotides representing a plurality of known genes derived from the two cell types, under conditions that result in hybridization of the cDNAs to complementary-sequence polynucleotides in the array. The array is then examined by fluorescence under fluorescence excitation conditions in which (i) polynucleotides in the array that are hybridized predominantly to cDNAs derived from one of the first or second cell types give a distinct first and second fluorescence emission color, respectively, and (ii) polynucleotides in the array that are hybridized to substantially equal numbers of cDNAs derived from the first and second cell types give a distinct combined fluorescence emission color, respectively. The relative expression of known genes in the two cell types can then be determined by the observed fluorescence emission color of each spot.

The Brown '522 patent further teaches that the "[m]icroarrays of immobilized nucleic acid sequences prepared in accordance with the invention" can be used in "numerous" genetic applications, including "monitoring of gene expression" applications (see Tab D at col. 14, lines 36-42). The Brown '522 patent teaches (a) monitoring gene expression (i) in different tissue types, (ii) in different disease states, and (iii) in response to different drugs, and (b) that arrays disclosed therein may be used in toxicology studies (see Tab D at col. 15, lines 13-18 and 52-58 and col. 18, lines 25-30).

13. Also pertinent to my considerations underlying this Declaration is the DeRisi article, published in December 1996. The DeRisi article describes the use of the Stanford-developed cDNA microarray technology "to analyze gene expression patterns in human cancer" (see Tab E at, e.g., p. 457). The DeRisi article specifically indicates, consistent with what was apparent to persons skilled in the art in December 1996, that increasing the number of genes on the cDNA microarray permits a "more comprehensive survey of gene expression patterns," thereby enhancing the ability of the cDNA microarray to provide "new and useful insights into human biology and a deeper understanding of the gene pathways involved in the pathogenesis of cancer and other diseases" (see Tab E at p. 458).

14. Other pre-June, 1999 publications further evidence the utility of the cDNA microarrays first developed at Stanford in a wide range of gene expression monitoring applications (see, e.g., the Shalon and the Heller articles at Tabs F and G). By no later than the March 1997 publication of the Heller article, these publications showed that employees of Synteni (i.e., James Gilmore and myself) had used the cDNA microarrays in specific gene expression monitoring applications (see Tab G).

The Heller article states that the results reported therein "successfully demonstrate the use of the cDNA microarray system as a general approach for dissecting human diseases" (Tab G at p. 2150). Among other things, the Heller article describes the investigation of "1000 human genes that were randomly selected from a peripheral human blood cell library" and "[t]heir differential and quantitative expression analysis in cells of the joint tissue. . . to demonstrate the utility of the microarray method to analyze complex diseases by their pattern of gene expression" (see Tab G at pp. 2150 *et seq.*).

Much of the work reported on in the Heller article was done in 1996. That article, therefore, evidences how persons skilled in the art were readily able, well prior to June 16, 1999, to make and use cDNA microarrays to achieve highly useful results. For example, as reported in the Heller article, a cDNA microarray that was used in some of the highly successful work reported on therein was made from 1,000 genes randomly selected from a human blood cell library.

15. A person skilled in the art on June 16, 1999, who read the Yue '566 application, would understand that application to disclose the SEQ ID NO:12-encoding polynucleotides, for example, SEQ ID NO:64, to be highly useful as probes for the expression of that specific polynucleotide in cDNA microarrays of the type first developed at Stanford. For example, the specification of the Yue '566 application would have led a person skilled in the art in June, 1999 who was using gene expression monitoring in connection with working on developing new drugs for the treatment of cancer, immune disorders, neurological disorders, and gastrointestinal disorders to conclude that a cDNA microarray that contained the SEQ ID NO:12-encoding polynucleotides would be a highly useful tool and to request specifically that any cDNA microarray that was being used for such purposes contain the SEQ ID NO:12-encoding polynucleotides. Persons skilled in the art would appreciate that cDNA microarrays that contained the SEQ ID NO:12-encoding polynucleotides would be a more useful tool than cDNA microarrays that did not contain the polynucleotides in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating cancer, immune disorders, neurological disorders, and gastrointestinal disorders for such purposes as evaluating their efficacy and toxicity.

I discuss in more detail in items (a)-(g) below a number of reasons why a person skilled in the art, who read the Yue '566 specification in June, 1999, would have concluded based on that specification and the state of the art at that time, that the SEQ ID NO:12-encoding polynucleotides would be a highly useful tool for inclusion in cDNA microarrays for evaluating the efficacy and toxicity of proposed drugs for treating cancer, immune disorders, neurological disorders, and gastrointestinal disorders, as well as for other evaluations:

(a) The Yue '566 application teaches the SEQ ID NO:12-encoding polynucleotides to be useful as probes in cDNA microarrays of the type first developed at Stanford. It also teaches that such cDNA microarrays are useful in a number of gene expression monitoring applications, including "developing and monitoring the activity of therapeutic agents [i.e., drugs]" (see paragraph 10, *supra*).

(b) By June, 1999, the Stanford-developed cDNA microarray technology was a well known and widely accepted tool for use in a wide range of gene expression monitoring applications. This is evidenced, for example, by numerous publications describing the use of that

cDNA technology in gene expression monitoring applications and the fact that, for over a year, the technology had provided the basis for the operations of an up-and-running company (Synteni), with employees, that was created for the purpose of developing and commercially exploiting that technology (see paragraphs 2, 8 and 10-14, *supra*). The fact that Incyte agreed to purchase Synteni in late 1997 for an amount reported to be at least about \$80 million only serves to underscore the substantial practical and commercial significance, in 1997, of the cDNA microarray technology first developed at Stanford (see paragraph 2, *supra*).

(c) The pre-June, 1999 publications regarding the cDNA microarray technology first developed at Stanford that I discuss in this Declaration repeatedly confirm that, consistent with the teachings in the Yue '566 application, cDNA microarrays are highly useful tools for conducting gene expression monitoring applications with respect to the development of drugs and the monitoring of their activity. Among other things, those pre-June, 1999 publications confirmed that cDNA microarrays (i) were useful for monitoring gene expression responses to different drugs (see paragraph 12, *supra*), (ii) were useful in analyzing gene expression patterns in human cancer, with increasing the number of genes on the cDNA microarray enhancing the ability of the cDNA microarray to provide useful information (see paragraph 13, *supra*), and (iii) were a valuable tool for use as part of a "general approach for dissecting human diseases" and for "analyz[ing] complex diseases by their pattern of gene expression" (see paragraph 14, *supra*).

(d) Based on my own extensive work for a company whose business was the development and commercial exploitation of cDNA microarray technology for more than two years prior to the June, 1999 filing date of the Yue '566 application, I have first-hand knowledge concerning the state of the art with respect to making and using cDNA microarrays as of June 16, 1999 (see paragraphs 2 and 14, *supra*). Persons skilled in the art as of that date would have (a) concluded that the Yue '566 application disclosed cDNA microarrays containing the SEQ ID NO:12-encoding polynucleotides to be useful, and (b) readily been able to make and use such microarrays with useful results.

(e) The Yue '566 specification contains a number of teachings that would lead persons skilled in the art on June 16, 1999 to conclude that a cDNA microarray that contained the SEQ ID NO:12-encoding polynucleotides would be a more useful tool for gene expression monitoring

applications relating to drugs for treating cancer, immune disorders, neurological disorders, and gastrointestinal disorders than a cDNA microarray that did not contain the SEQ ID NO:12-encoding polynucleotides. Among other things, the Yue '566 specification teaches that the identity of the SEQ ID NO:64 polynucleotide was determined from a diseased gallbladder cDNA library (GBLANOT01) (Yue '566 application, Table 4). Moreover, northern analysis of SEQ ID NO:64 shows its expression predominantly in cDNA libraries associated with reproductive, gastrointestinal, and nervous system tissues and in tissues associated with cancer and inflammation. (Yue '566 application at Table 3). (See paragraph 9, *supra*).

Moreover, the Yue '566 specification teaches that the INSIG protein having the amino acid sequence of SEQ ID NO:12 shares homology with known functional proteins. INSIG-12 is a member of the annexin protein family. In particular, SEQ ID NO:12 shares homology with the sequence of the non-CD4 glycoprotein gp120 receptor (GENESEQ AAR32188). (Yue '566 application, at Table 2).

(f) Persons skilled in the art on June 16, 1999 would have appreciated (i) that the gene expression monitoring results obtained using a cDNA microarray containing a probe to a sequence selected from the group consisting of SEQ ID NO:12-encoding polynucleotides would vary, depending on the particular drug being evaluated, and (ii) that such varying results would occur both with respect to the results obtained from the probe described in (i) and from the cDNA microarray as a whole (including all its other individual probes). These kinds of varying results, depending on the identity of the drug being tested, in no way detracts from my conclusion that persons skilled in the art on June 16, 1999, having read the Yue '566 specification, would specifically request that any cDNA microarray that was being used for conducting gene expression monitoring studies on drugs for treating cancer, immune disorders, neurological disorders, and gastrointestinal disorders (*e.g.*, a toxicology study or any efficacy study of the type that typically takes place in connection with the development of a drug) contain any one of the SEQ ID NO:12-encoding polynucleotides as a probe. Persons skilled in the art on June 16, 1999 would have wanted their cDNA microarray to have a probe as described in (i) because a microarray that contained such a probe (as compared to one that did not) would provide more useful results in the kind of gene expression monitoring studies using cDNA microarrays that persons skilled in the art have been doing since well prior to June 16, 1999.

The foregoing is not intended to be an all-inclusive explanation of all my reasons for reaching the conclusions stated in this paragraph 15, and in paragraph 6, *supra*. In my view, however, it provides more than sufficient reasons to justify my conclusions stated in paragraph 6 of this Declaration regarding the Yue '566 application disclosing to persons skilled in the art at the time of its filing substantial, specific and credible real-world utilities for the SEQ ID NO:12-encoding polynucleotides.

16. Also pertinent to my considerations underlying this Declaration is the fact that the Yue '566 disclosure regarding the uses of the SEQ ID NO:64 polynucleotide for gene expression monitoring applications is not limited to the use of that polynucleotide as a probe in microarrays. For one thing, the Yue '566 disclosure regarding the hybridization technique used in gene expression monitoring applications is broad (Yue '566 application at, e.g., p. 4, lines 2-8).

In addition, the Yue '566 specification repeatedly teaches that the polynucleotides described therein (including the polynucleotide of SEQ ID NO:64) may desirably be used as probes in any of a number of long established "standard" non-microarray techniques, such as Northern analysis, for conducting gene expression monitoring studies. See, e.g.:

- (a) Yue '566 application at p. 8, lines 21-24 ("[N]orthern analysis is indicative of the presence of nucleic acids encoding INSIG in a sample, and thereby correlates with expression of the transcript from the polynucleotide encoding INSIG");
- (b) Yue '566 application at p. 32, line 35 through p. 33, line 3 ("The polynucleotide sequences encoding INSIG may be used in Southern or northern analysis, dot blot, or other membrane-based technologies; in PCR technologies; in dipstick, pin, and multiformat ELISA-like assays; and in microarrays utilizing fluids or tissues from patients to detect altered INSIG expression. Such qualitative or quantitative methods are well known in the art");
- (c) Yue '566 application at p. 33, lines 14-22 ("In order to provide a basis for the diagnosis of a disorder associated with expression of INSIG, a normal or standard profile for expression is established. This may be accomplished by combining body fluids or cell extracts taken from normal subjects, either animal or human, with a sequence, or a fragment thereof, encoding INSIG, under conditions suitable for hybridization or amplification. Standard hybridization may be quantified by

comparing the values obtained from normal subjects with values from an experiment in which a known amount of a substantially purified polynucleotide is used. Standard values obtained in this manner may be compared with values obtained from samples from patients who are symptomatic for a disorder.

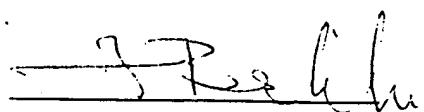
Deviation from standard values is used to establish the presence of a disorder"); and

(d) Yue '566 application at p. 38, lines 14-18 ("Northern analysis is a laboratory technique used to detect the presence of a transcript of a gene and involves the hybridization of a labeled nucleotide sequence to a membrane on which RNAs from a particular cell type or tissue have been bound. (See, e.g., Sambrook, supra, ch. 7; Ausubel, 1995, supra, ch. 4 and 16.)").

The "Sambrook et al." reference cited in item (d) immediately above is a reference that was well known to persons skilled in the art in June, 1999. A copy of pages from that reference manual, which was published in 1989, is annexed to this Declaration at Tab H. The attached pages from the Sambrook manual provide an overview of northern analysis and other membrane-based technologies for conducting gene expression monitoring studies that were known and used by persons skilled in the art for many years prior to the June 16, 1999 filing date of the Yue '566 application.

A person skilled in the art on June 16, 1999, who read the Yue '566 specification, would have routinely and readily appreciated that the SEQ ID NO:12-encoding polynucleotides disclosed therein would be useful as a probe to conduct gene expression monitoring analyses using northern analysis or any of the other traditional membrane-based gene expression monitoring techniques that were known and in common use many years prior to the filing of the Yue '566 application. For example, a person skilled in the art in June, 1999 would have routinely and readily appreciated that the SEQ ID NO:12-encoding polynucleotides would be a useful tool in conducting gene expression analyses, using the northern analysis technique, in furtherance of (a) the development of drugs for the treatment of cancer, immune disorders, neurological disorders, and gastrointestinal disorders, and (b) analyses of the efficacy and toxicity of such drugs.

17. I declare further that all statements made herein of my own knowledge are true and that all statements made herein on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, and that willful false statements may jeopardize the validity of this application and any patent issuing thereon.



Tod Bedilion

Signed at Redwood City, California  
this 21<sup>st</sup> day of April, 2003

*[Signature]* Certificate of Mailing  
I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed  
to: Mail Stop: Non-Fee Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on May 1, 2003.  
By: [Signature] Printed: \_\_\_\_\_

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of: Yue et al.

Title: INTRACELLULAR SIGNALING MOLECULES

Serial No.: 10/018,170 Filing Date: December 11, 2001

Examiner: Steadman, D Group Art Unit: 1652

Mail Stop: Non-Fee Amendment  
Commissioner for Patents  
P. O. Box 1450  
Alexandria, VA 22313-1450

**DECLARATION OF DR. TOD BEDILION**  
UNDER 37 C.F.R. § 1.132

I, TOD BEDILION, a citizen of the United States, residing at 132 Winding Way, San Carlos, California, declare that:

1. I was employed by Incyte Genomics, Inc. (hereinafter "Incyte") as a Director of Corporate Development until May 11, 2001. I am currently under contract to be a Consultant to Incyte Genomics, Inc.

2. In 1996, I received a Ph.D. degree in Cell, Molecular and Development Biology from UCLA. I had previously received, in 1988, a B.S. degree in biology from UCLA.

Upon my graduation from UCLA, I became, in April 1996, the first employee of Synteni, Inc. (hereinafter "Synteni"). I was a Research Director at Synteni from April 1996 until Synteni was acquired by Incyte in early 1998.

I understand that Synteni was founded in 1994 by T. Dari Shalon while he was a graduate student at Stanford University. I further understand that Synteni was founded for the purpose

of commercially exploiting certain "cDNA microarray" technology that was being worked on at Stanford in the early to mid-1990s. That technology, which I will sometimes refer to herein as the "Stanford-developed cDNA microarray technology", was the subject of Dr. Shalon's doctoral thesis at Stanford. I understand and believe that Dr. P.O. Brown was Dr. Shalon's thesis advisor at Stanford.

During the period beginning before I was employed by Synteni and ending upon its acquisition by Incyte in early 1998, I understand Synteni was the exclusive licensee of the Stanford-developed cDNA microarray technology, subject to any right that the United States government may have with respect to that technology. In early 1998, I understand Incyte acquired rights under the Stanford-developed cDNA microarray technology as part of its acquisition of Synteni.

I understand that at the time of the commencement of my employment at Synteni in April 1996, Synteni's rights with respect to the Stanford-developed cDNA technology included rights under a United States patent application that had been filed June 7, 1995 in the names of Drs. Brown and Shalon and that subsequently issued as United States Patent No. 5,807,522 (the Brown '522 patent). In December 1995, the subject matter of the Brown '522 patent was published based on a PCT patent application that had also been filed in June 1995. The Brown '522 patent (and its corresponding PCT application) describes the use of the Stanford-developed cDNA technology in a number of gene expression monitoring applications, as will be discussed more fully below.

Upon Incyte's acquisition of Synteni, I became employed by Incyte. From early 1998 until late 1999, I was an Associate Research Director at Incyte. In late 1999, I was promoted to the position of Director, Corporate Development.

I have been aware of the Stanford-developed cDNA microarray technology since shortly before I commenced my employment at Synteni. While I was employed by Synteni, virtually all (if not all) of my work efforts (as well as the work efforts of others employed by Synteni) were directed to the further development and commercial exploitation of that cDNA microarray technology. By the end of 1997, those efforts had progressed to the point that I understand Incyte agreed to pay at least about \$80 million to acquire Synteni. Since I have been employed by Incyte, I have continued to work

on the further development and commercial exploitation of the cDNA microarray technology that was first developed at Stanford in the early to mid-1990s.

3. I have reviewed the specification of a United States patent application that I understand was filed on December 11, 2001 in the names of Yue et al. and was assigned Serial No. 10/018,170 (hereinafter "the Yue '170 application"). Furthermore, I understand that this United States patent application claimed priority to United States Provisional Patent Application Serial No. 60/139,566 filed on June 16, 1999 (hereinafter "the Yue '566 application"). The SEQ ID NO:12-encoding polynucleotides were described in the Yue '566 application. (Note that the sequences of SEQ ID NO:12 and SEQ ID NO:64 disclosed in the Yue '170 application are identical to the sequences referred to as SEQ ID NO:12 and SEQ ID NO:31, respectively, in the Yue '566 application). My remarks herein will therefore be directed to the Yue '566 patent application, and June 16, 1999, as the relevant date of filing. In broad overview, the Yue '566 specification pertains to certain nucleotide and amino acid sequences and their use in a number of applications, including gene expression monitoring applications that are useful in connection with (a) developing drugs (e.g., the diagnosis of inherited and acquired genetic disorders, expression profiling, toxicology testing, and drug development with respect to cancer, an immunopathology, a neuropathology, and the like), and (b) monitoring the activity of drugs for purposes relating to evaluating their efficacy and toxicity.

4. I understand that (a) the Yue '566 application contains claims that are directed to isolated and purified polynucleotides having the sequences disclosed in the Yue '170 application as SEQ ID NO:12-encoding polynucleotides, for example SEQ ID NO:64 (hereinafter "the SEQ ID NO:12-encoding polynucleotides"), and (b) the Patent Examiner has rejected those claims on the grounds that the specification of the Yue '566 application does not disclose a substantial, specific and credible utility for the claimed SEQ ID NO:12-encoding polynucleotides. I further understand that whether or not a patent specification discloses a substantial, specific and credible utility for its claimed subject matter is properly determined from the perspective of a person skilled in the art to which the specification pertains at the time of the patent application was filed. In addition, I understand that a substantial, specific and credible utility under the patent laws must be a "real-world" utility.

5. I have been asked (a) to consider with a view to reaching a conclusion (or conclusions) as to whether or not I agree with the Patent Examiner's position that the Yue '566 application does not disclose a substantial, specific and credible "real-world" utility for the claimed SEQ ID NO:12-encoding polynucleotides, and (b) to state and explain the bases for any conclusions I reach. I have been informed that, in connection with my considerations, I should determine whether or not a person skilled in the art to which the Yue '566 application pertains on June 16, 1999 would have concluded that the Yue '566 application disclosed, for the benefit of the public, a specific beneficial use of the SEQ ID NO:12-encoding polynucleotides in their then available and disclosed form. I have also been informed that, with respect to the "real-world" utility requirement, the Patent and Trademark Office instructs its Patent Examiners in Section 2107 of the Manual of Patent Examining Procedure, under the heading "I. 'Real-World Value' Requirement":

"Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact 'useful' in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified utility and inventions whose specific utility requires further research to identify or reasonably confirm."

6. I have considered the matters set forth in paragraph 5 of this Declaration and have concluded that, contrary to the position I understand the Patent Examiner has taken, the specification of the Yue '566 patent application disclosed to a person skilled in the art at the time of its filing a number of substantial, specific and credible real-world utilities for the claimed SEQ ID NO:12-encoding polynucleotides. More specifically, persons skilled in the art on June 16, 1999 would have understood the Yue '566 application to disclose the use of the SEQ ID NO:12-encoding polynucleotides in a number of gene expression monitoring applications that were well-known at that time to be useful in connection with the development of drugs and the monitoring of the activity of such drugs. I explain the bases for reaching my conclusion in this regard in paragraphs 7-16 below.

7. In reaching the conclusion stated in paragraph 6 of this Declaration, I considered (a) the specification of the Yue '566 application, and (b) a number of published articles and patent documents that evidence gene expression monitoring techniques that were well-known before the June 16, 1999 filing date of the Yue '566 application. The published articles and patent documents I considered are:

- (a) Schena, M., Shalon, D., Heller, R., Chai, A., Brown, P.O., and Davis, R.W., Parallel human genome analysis: Microarray-based expression monitoring of 1000 genes, Proc. Natl. Acad. Sci. USA, 93, 10614-10619 (1996) (hereinafter "the Schena 1996 article") (copy annexed at Tab A);
- (b) Schena, M., Shalon, D., Davis, R.W., Brown, P.O., Quantitative Monitoring of Gene Expression Patterns with a Complementary DNA Microarray, Science, 270, 467-470 (1995) (hereinafter "the Schena 1995 article") (copy annexed at Tab B);
- (c) Shalon and Brown PCT patent application WO 95/35505 titled "Method and Apparatus For Fabricating Microarrays Of Biological Samples," filed on June 16, 1995, and published on December 28, 1995 (hereinafter "the Shalon PCT application") (copy annexed at Tab C);
- (d) Brown and Shalon U.S. Patent No. 5,807,522, corresponding to the Shalon PCT application, titled "Methods For Fabricating Microarrays Of Biological Samples," filed on June 7, 1995 and issued on September 15, 1998 (hereinafter "the Brown '522 patent") (copy annexed at Tab D);
- (e) DeRisi, J., Penland, L., and Brown, P.O. (Group 1); Bittner, M.L., Meltzer, P.S., Ray, M., Chen, Y., Su, Y.A., and Trent, J.M. (Group 2), Use of a cDNA microarray to analyse gene expression patterns in human cancer, Nat. Genet., 14(4), 457-460 (1996) (hereinafter "the DeRisi article") (copy annexed at Tab E);
- (f) Shalon, D., Smith, S.J., and Brown, P.O., A DNA Microarray System for Analyzing Complex DNA Samples Using Two-color Fluorescent Probe Hybridization, Genome Res., 6(7), 639-645 (1996) (hereinafter "the Shalon article") (copy annexed at Tab F);
- (g) Heller, R.A., Schena, M., Chai A., Shalon, D., Bedilion, T., Gilmore, J., Woolley, D.E., and Davis R.W., Discovery and analysis of inflammatory disease-related genes using

cDNA microarrays, Proc. Natl. Acad. Sci. USA, 94, 2150-2155 (1997) (hereinafter “the Heller article”)(copy annexed at Tab G);

(h) Sambrook, J., Fritsch, E.F., Maniatis, T., Molecular Cloning, A Laboratory Manual, pages 7.37 and 7.38, Cold Spring Harbor Press (1989) (hereinafter “the Sambrook Manual”) (copy annexed at Tab H);

8. Many of the published articles and patent documents I considered (i.e., at least items (a)-(g) identified in paragraph 7) relate to work done at Stanford University in the early and mid-1990s with respect to the development of cDNA microarrays for use in gene expression monitoring applications under which Synteni became exclusively licensed. As I will discuss, a person skilled in the art who read the Yue ‘566 application on June 16, 1999 would have understood that application to disclose the SEQ ID NO:12-encoding polynucleotides to be useful for a number of gene expression monitoring applications, e.g., as a probe for the expression of that specific polynucleotide in cDNA microarrays of the type first developed at Stanford.

9. Turning more specifically to the Yue ‘566 specification, the SEQ ID NO:64 polynucleotide (referred to as SEQ ID NO:31 in the Yue ‘566 application) is shown at p. 33 as one of 38 sequences under the heading “Sequence Listing.” The Yue ‘566 specification specifically teaches that the invention provides isolated and purified polynucleotides that encode INSIG (Yue ‘566 application at p. 3). It further teaches that (a) the identity of the SEQ ID NO:64 polynucleotide was determined from a diseased gallbladder tissue cDNA library (GBLANOT01) (Yue ‘566 application, Table 4), (b) the SEQ ID NO:64 polynucleotide encodes for the annexin protein (INSIG) shown as SEQ ID NO:12 (Yue ‘566 application at Tables 1 and 2), and (c) northern analysis of SEQ ID NO:64 shows its expression predominantly in cDNA libraries associated with reproductive, gastrointestinal, and nervous system tissues and in tissues associated with cancer and inflammation (Yue ‘566 application at Table 4).

The Yue ‘566 application discusses a number of uses of the SEQ ID NO:12-encoding polynucleotides in addition to their use in gene expression monitoring applications. I have not fully evaluated these additional uses in connection with the preparation of this Declaration and do not express any views in this Declaration regarding whether or not the Yue ‘566 specification discloses

these additional uses to be substantial, specific and credible real-world utilities of the SEQ ID NO:12-encoding polynucleotides. Consequently, my discussion in this Declaration concerning the Yue '566 application focuses on the portions of the application that relate to the use of the SEQ ID NO:12-encoding polynucleotides in gene expression monitoring applications.

10. The Yue '566 application discloses that the polynucleotide sequences disclosed therein, including the SEQ ID NO:12-encoding polynucleotides, are useful as probes in microarrays. It further teaches that the microarrays can be used "to monitor the expression level of large numbers of genes simultaneously" for a number of purposes, including "to develop and monitor the activities of therapeutic agents" (Yue '566 application at p. 34, lines 10-15).

In the paragraph immediately following the Yue '566 teachings described in the preceding paragraph of this Declaration, the Yue '566 application teaches that microarrays can be prepared using the previously mentioned cDNA microarray technology developed at Stanford in the early to mid-1990s. In this connection, the Yue '566 application specifically cites to the Schena 1996 article identified in item (a) of paragraph 7 of this Declaration (Yue '566 application at p. 34; *supra*, paragraph 7).

The Schena 1996 article is one of a number of documents that were published prior to the June 16, 1999 filing date of the Yue '566 application that describes the use of the Stanford-developed cDNA technology in a wide range of gene expression monitoring applications, including monitoring and analyzing gene expression patterns in human cancer. In view of the Yue '566 application, the Schena 1996 article, and other related pre-June, 1999 publications, persons skilled in the art on June 16, 1999 clearly would have understood the Yue '566 application to disclose the SEQ ID NO:12-encoding polynucleotides to be useful in cDNA microarrays for the development of new drugs and monitoring the activities of drugs for such purposes as evaluating their efficacy and toxicity, as explained more fully in paragraph 15 below.

With specific reference to toxicity evaluations, those of skill in the art who were working on drug development in June, 1999 (and for many years prior to June, 1999) without any doubt appreciated that the toxicity (or lack of toxicity) of any proposed drug they were working on was one of the most important criteria to be considered and evaluated in connection with the development

of the drug. They would have understood at that time that good drugs are not only potent, they are specific. This means that they have strong effects on a specific biological target and minimal effects on all other biological targets. Ascertaining that a candidate drug affects its intended target, and identification of undesirable secondary effects (i.e., toxic side effects), had been for many years among the main challenges in developing new drugs. The ability to determine which genes are positively affected by a given drug, coupled with the ability to quickly and at the earliest time possible in the drug development process identify drugs that are likely to be toxic because of their undesirable secondary effects, have enormous value in improving the efficiency of the drug discovery process, and are an important and essential part of the development of any new drug. Accordingly, the teachings in the Yue '566 application, in particular regarding use of the SEQ ID NO:12-encoding polynucleotides in differential gene expression analysis and in the development and the monitoring of the activities of drugs, clearly includes toxicity studies and persons skilled in the art who read the Yue '566 application on June 16, 1999 would have understood that to be so.

11. The Schena 1996 article was not the first publication that described the use of the cDNA microarray technique developed at Stanford to monitor quantitatively gene expression patterns. More than a year earlier (i.e., in October 1995), the Schena 1995 article, titled "Quantitative Monitoring of Gene Expression Patterns with a Complementary DNA Microarray", was published (see Tabs A and B).

12. As previously discussed (*supra*, paragraphs 2 and 7), in the mid-1990s patent applications were filed in the names of Drs. Shalon and Brown that described the Stanford-developed cDNA microarray technology. The two patent documents (i.e., the Shalon PCT application and the Brown '522 patent) annexed to this Declaration at Tabs C and D evidence information that was available to the public regarding the Stanford-developed cDNA microarray technology before the June 16, 1999 filing date of the Yue '566 application.

The Shalon PCT patent application, which was published in December 1995, contains virtually the same (if not exactly the same) specification as the Brown '522 patent. Hence, the Brown '522 patent disclosure was, in effect, available to the public as of the December 1995 publication date

of the Shalon PCT application(see Tabs C and D). For the sake of convenience, I cite to and discuss the Brown '522 specification below on the understanding that the descriptions in that specification were published as of the December 28, 1995 publication date of the Shalon PCT application.

The Brown '522 patent discusses, in detail, the utility of the Stanford-developed cDNA microarrays in gene expression monitoring applications. For example, in the "Summary Of The Invention" section, the Brown '522 patent teaches (see Tab D, col. 4, line 52-col. 5, line 8):

Also forming part of the invention is a method of detecting differential expression of each of a plurality of genes in a first cell type, with respect to expression of the same genes in a second cell type. In practicing the method, there is first produced fluorescent-labeled cDNAs from mRNAs isolated from two cells types, where the cDNAs from the first and second cell types are labeled with first and second different fluorescent reporters.

A mixture of the labeled cDNAs from the two cell types is added to an array of polynucleotides representing a plurality of known genes derived from the two cell types, under conditions that result in hybridization of the cDNAs to complementary-sequence polynucleotides in the array. The array is then examined by fluorescence under fluorescence excitation conditions in which (i) polynucleotides in the array that are hybridized predominantly to cDNAs derived from one of the first or second cell types give a distinct first and second fluorescence emission color, respectively, and (ii) polynucleotides in the array that are hybridized to substantially equal numbers of cDNAs derived from the first and second cell types give a distinct combined fluorescence emission color, respectively. The relative expression of known genes in the two cell types can then be determined by the observed fluorescence emission color of each spot.

The Brown '522 patent further teaches that the "[m]icroarrays of immobilized nucleic acid sequences prepared in accordance with the invention" can be used in "numerous" genetic applications, including "monitoring of gene expression" applications (see Tab D at col. 14, lines 36-42). The Brown '522 patent teaches (a) monitoring gene expression (i) in different tissue types, (ii) in different disease states, and (iii) in response to different drugs, and (b) that arrays disclosed therein may be used in toxicology studies (see Tab D at col. 15, lines 13-18 and 52-58 and col. 18, lines 25-30).

13. Also pertinent to my considerations underlying this Declaration is the DeRisi article, published in December 1996. The DeRisi article describes the use of the Stanford-developed cDNA microarray technology "to analyze gene expression patterns in human cancer" (see Tab E at, e.g., p. 457). The DeRisi article specifically indicates, consistent with what was apparent to persons skilled in the art in December 1996, that increasing the number of genes on the cDNA microarray permits a "more comprehensive survey of gene expression patterns," thereby enhancing the ability of the cDNA microarray to provide "new and useful insights into human biology and a deeper understanding of the gene pathways involved in the pathogenesis of cancer and other diseases" (see Tab E at p. 458).

14. Other pre-June, 1999 publications further evidence the utility of the cDNA microarrays first developed at Stanford in a wide range of gene expression monitoring applications (see, e.g., the Shalon and the Heller articles at Tabs F and G). By no later than the March 1997 publication of the Heller article, these publications showed that employees of Synteni (i.e., James Gilmore and myself) had used the cDNA microarrays in specific gene expression monitoring applications (see Tab G).

The Heller article states that the results reported therein "successfully demonstrate the use of the cDNA microarray system as a general approach for dissecting human diseases" (Tab G at p. 2150). Among other things, the Heller article describes the investigation of "1000 human genes that were randomly selected from a peripheral human blood cell library" and "[t]heir differential and quantitative expression analysis in cells of the joint tissue . . . to demonstrate the utility of the microarray method to analyze complex diseases by their pattern of gene expression" (see Tab G at pp. 2150 *et seq.*).

Much of the work reported on in the Heller article was done in 1996. That article, therefore, evidences how persons skilled in the art were readily able, well prior to June 16, 1999, to make and use cDNA microarrays to achieve highly useful results. For example, as reported in the Heller article, a cDNA microarray that was used in some of the highly successful work reported on therein was made from 1,000 genes randomly selected from a human blood cell library.

15. A person skilled in the art on June 16, 1999, who read the Yue '566 application, would understand that application to disclose the SEQ ID NO:12-encoding polynucleotides, for example, SEQ ID NO:64, to be highly useful as probes for the expression of that specific polynucleotide in cDNA microarrays of the type first developed at Stanford. For example, the specification of the Yue '566 application would have led a person skilled in the art in June, 1999 who was using gene expression monitoring in connection with working on developing new drugs for the treatment of cancer, immune disorders, neurological disorders, and gastrointestinal disorders to conclude that a cDNA microarray that contained the SEQ ID NO:12-encoding polynucleotides would be a highly useful tool and to request specifically that any cDNA microarray that was being used for such purposes contain the SEQ ID NO:12-encoding polynucleotides. Persons skilled in the art would appreciate that cDNA microarrays that contained the SEQ ID NO:12-encoding polynucleotides would be a more useful tool than cDNA microarrays that did not contain the polynucleotides in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating cancer, immune disorders, neurological disorders, and gastrointestinal disorders for such purposes as evaluating their efficacy and toxicity.

I discuss in more detail in items (a)-(g) below a number of reasons why a person skilled in the art, who read the Yue '566 specification in June, 1999, would have concluded based on that specification and the state of the art at that time, that the SEQ ID NO:12-encoding polynucleotides would be a highly useful tool for inclusion in cDNA microarrays for evaluating the efficacy and toxicity of proposed drugs for treating cancer, immune disorders, neurological disorders, and gastrointestinal disorders, as well as for other evaluations:

(a) The Yue '566 application teaches the SEQ ID NO:12-encoding polynucleotides to be useful as probes in cDNA microarrays of the type first developed at Stanford. It also teaches that such cDNA microarrays are useful in a number of gene expression monitoring applications, including "developing and monitoring the activity of therapeutic agents [i.e., drugs]" (see paragraph 10, *supra*).

(b) By June, 1999, the Stanford-developed cDNA microarray technology was a well known and widely accepted tool for use in a wide range of gene expression monitoring applications. This is evidenced, for example, by numerous publications describing the use of that

cDNA technology in gene expression monitoring applications and the fact that, for over a year, the technology had provided the basis for the operations of an up-and-running company (Synteni), with employees, that was created for the purpose of developing and commercially exploiting that technology (see paragraphs 2, 8 and 10-14, *supra*). The fact that Incyte agreed to purchase Synteni in late 1997 for an amount reported to be at least about \$80 million only serves to underscore the substantial practical and commercial significance, in 1997, of the cDNA microarray technology first developed at Stanford (see paragraph 2, *supra*).

(c) The pre-June, 1999 publications regarding the cDNA microarray technology first developed at Stanford that I discuss in this Declaration repeatedly confirm that, consistent with the teachings in the Yue '566 application, cDNA microarrays are highly useful tools for conducting gene expression monitoring applications with respect to the development of drugs and the monitoring of their activity. Among other things, those pre-June, 1999 publications confirmed that cDNA microarrays (i) were useful for monitoring gene expression responses to different drugs (see paragraph 12, *supra*), (ii) were useful in analyzing gene expression patterns in human cancer, with increasing the number of genes on the cDNA microarray enhancing the ability of the cDNA microarray to provide useful information (see paragraph 13, *supra*), and (iii) were a valuable tool for use as part of a "general approach for dissecting human diseases" and for "analyz[ing] complex diseases by their pattern of gene expression" (see paragraph 14, *supra*).

(d) Based on my own extensive work for a company whose business was the development and commercial exploitation of cDNA microarray technology for more than two years prior to the June, 1999 filing date of the Yue '566 application, I have first-hand knowledge concerning the state of the art with respect to making and using cDNA microarrays as of June 16, 1999 (see paragraphs 2 and 14, *supra*). Persons skilled in the art as of that date would have (a) concluded that the Yue '566 application disclosed cDNA microarrays containing the SEQ ID NO:12-encoding polynucleotides to be useful, and (b) readily been able to make and use such microarrays with useful results.

(e) The Yue '566 specification contains a number of teachings that would lead persons skilled in the art on June 16, 1999 to conclude that a cDNA microarray that contained the SEQ ID NO:12-encoding polynucleotides would be a more useful tool for gene expression monitoring

applications relating to drugs for treating cancer, immune disorders, neurological disorders, and gastrointestinal disorders than a cDNA microarray that did not contain the SEQ ID NO:12-encoding polynucleotides. Among other things, the Yue '566 specification teaches that the identity of the SEQ ID NO:64 polynucleotide was determined from a diseased gallbladder cDNA library (GBLANOT01) (Yue '566 application, Table 4). Moreover, northern analysis of SEQ ID NO:64 shows its expression predominantly in cDNA libraries associated with reproductive, gastrointestinal, and nervous system tissues and in tissues associated with cancer and inflammation. (Yue '566 application at Table 3). (See paragraph 9, *supra*).

Moreover, the Yue '566 specification teaches that the INSIG protein having the amino acid sequence of SEQ ID NO:12 shares homology with known functional proteins. INSIG-12 is a member of the annexin protein family. In particular, SEQ ID NO:12 shares homology with the sequence of the non-CD4 glycoprotein gp120 receptor (GENESEQ AAR32188). (Yue '566 application, at Table 2).

(f) Persons skilled in the art on June 16, 1999 would have appreciated (i) that the gene expression monitoring results obtained using a cDNA microarray containing a probe to a sequence selected from the group consisting of SEQ ID NO:12-encoding polynucleotides would vary, depending on the particular drug being evaluated, and (ii) that such varying results would occur both with respect to the results obtained from the probe described in (i) and from the cDNA microarray as a whole (including all its other individual probes). These kinds of varying results, depending on the identity of the drug being tested, in no way detracts from my conclusion that persons skilled in the art on June 16, 1999, having read the Yue '566 specification, would specifically request that any cDNA microarray that was being used for conducting gene expression monitoring studies on drugs for treating cancer, immune disorders, neurological disorders, and gastrointestinal disorders (*e.g.*, a toxicology study or any efficacy study of the type that typically takes place in connection with the development of a drug) contain any one of the SEQ ID NO:12-encoding polynucleotides as a probe. Persons skilled in the art on June 16, 1999 would have wanted their cDNA microarray to have a probe as described in (i) because a microarray that contained such a probe (as compared to one that did not) would provide more useful results in the kind of gene expression monitoring studies using cDNA microarrays that persons skilled in the art have been doing since well prior to June 16, 1999.

The foregoing is not intended to be an all-inclusive explanation of all my reasons for reaching the conclusions stated in this paragraph 15, and in paragraph 6, *supra*. In my view, however, it provides more than sufficient reasons to justify my conclusions stated in paragraph 6 of this Declaration regarding the Yue '566 application disclosing to persons skilled in the art at the time of its filing substantial, specific and credible real-world utilities for the SEQ ID NO:12-encoding polynucleotides.

16. Also pertinent to my considerations underlying this Declaration is the fact that the Yue '566 disclosure regarding the uses of the SEQ ID NO:64 polynucleotide for gene expression monitoring applications is not limited to the use of that polynucleotide as a probe in microarrays. For one thing, the Yue '566 disclosure regarding the hybridization technique used in gene expression monitoring applications is broad (Yue '566 application at, e.g., p. 4, lines 2-8).

In addition, the Yue '566 specification repeatedly teaches that the polynucleotides described therein (including the polynucleotide of SEQ ID NO:64) may desirably be used as probes in any of a number of long established "standard" non-microarray techniques, such as Northern analysis, for conducting gene expression monitoring studies. See, e.g.:

(a) Yue '566 application at p. 8, lines 21-24 ("[N]orthern analysis is indicative of the presence of nucleic acids encoding INSIG in a sample, and thereby correlates with expression of the transcript from the polynucleotide encoding INSIG");

(b) Yue '566 application at p. 32, line 35 through p. 33, line 3 ("The polynucleotide sequences encoding INSIG may be used in Southern or northern analysis, dot blot, or other membrane-based technologies; in PCR technologies; in dipstick, pin, and multiformat ELISA-like assays; and in microarrays utilizing fluids or tissues from patients to detect altered INSIG expression. Such qualitative or quantitative methods are well known in the art");

(c) Yue '566 application at p. 33, lines 14-22 ("In order to provide a basis for the diagnosis of a disorder associated with expression of INSIG, a normal or standard profile for expression is established. This may be accomplished by combining body fluids or cell extracts taken from normal subjects, either animal or human, with a sequence, or a fragment thereof, encoding INSIG, under conditions suitable for hybridization or amplification. Standard hybridization may be quantified by

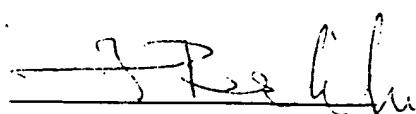
comparing the values obtained from normal subjects with values from an experiment in which a known amount of a substantially purified polynucleotide is used. Standard values obtained in this manner may be compared with values obtained from samples from patients who are symptomatic for a disorder. Deviation from standard values is used to establish the presence of a disorder"); and

(d) Yue '566 application at p. 38, lines 14-18 ("Northern analysis is a laboratory technique used to detect the presence of a transcript of a gene and involves the hybridization of a labeled nucleotide sequence to a membrane on which RNAs from a particular cell type or tissue have been bound. (See, e.g., Sambrook, supra, ch. 7; Ausubel, 1995, supra, ch. 4 and 16.)").

The "Sambrook et al." reference cited in item (d) immediately above is a reference that was well known to persons skilled in the art in June, 1999. A copy of pages from that reference manual, which was published in 1989, is annexed to this Declaration at Tab H. The attached pages from the Sambrook manual provide an overview of northern analysis and other membrane-based technologies for conducting gene expression monitoring studies that were known and used by persons skilled in the art for many years prior to the June 16, 1999 filing date of the Yue '566 application.

A person skilled in the art on June 16, 1999, who read the Yue '566 specification, would have routinely and readily appreciated that the SEQ ID NO:12-encoding polynucleotides disclosed therein would be useful as a probe to conduct gene expression monitoring analyses using northern analysis or any of the other traditional membrane-based gene expression monitoring techniques that were known and in common use many years prior to the filing of the Yue '566 application. For example, a person skilled in the art in June, 1999 would have routinely and readily appreciated that the SEQ ID NO:12-encoding polynucleotides would be a useful tool in conducting gene expression analyses, using the northern analysis technique, in furtherance of (a) the development of drugs for the treatment of cancer, immune disorders, neurological disorders, and gastrointestinal disorders, and (b) analyses of the efficacy and toxicity of such drugs.

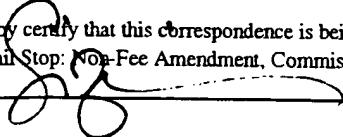
17. I declare further that all statements made herein of my own knowledge are true and that all statements made herein on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, and that willful false statements may jeopardize the validity of this application and any patent issuing thereon.



Tod Bedilion

Signed at Redwood City, California

this 21<sup>st</sup> day of April, 2003

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop: Non-Fee Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on May 1, 2003.  
By:  Printed: \_\_\_\_\_

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of: Yue et al.

Title: INTRACELLULAR SIGNALING MOLECULES

Serial No.: 10/018,170 Filing Date: December 11, 2001

Examiner: Steadman, D Group Art Unit: 1652

Mail Stop: Non-Fee Amendment  
Commissioner for Patents  
P. O. Box 1450  
Alexandria, VA 22313-1450

**DECLARATION OF DR. TOD BEDILION**  
**UNDER 37 C.F.R. § 1.132**

I, TOD BEDILION, a citizen of the United States, residing at 132 Winding Way, San Carlos, California, declare that:

1. I was employed by Incyte Genomics, Inc. (hereinafter "Incyte") as a Director of Corporate Development until May 11, 2001. I am currently under contract to be a Consultant to Incyte Genomics, Inc.

2. In 1996, I received a Ph.D. degree in Cell, Molecular and Development Biology from UCLA. I had previously received, in 1988, a B.S. degree in biology from UCLA.

Upon my graduation from UCLA, I became, in April 1996, the first employee of Synteni, Inc. (hereinafter "Synteni"). I was a Research Director at Synteni from April 1996 until Synteni was acquired by Incyte in early 1998.

I understand that Synteni was founded in 1994 by T. Dari Shalon while he was a graduate student at Stanford University. I further understand that Synteni was founded for the purpose

of commercially exploiting certain "cDNA microarray" technology that was being worked on at Stanford in the early to mid-1990s. That technology, which I will sometimes refer to herein as the "Stanford-developed cDNA microarray technology", was the subject of Dr. Shalon's doctoral thesis at Stanford. I understand and believe that Dr. P.O. Brown was Dr. Shalon's thesis advisor at Stanford.

During the period beginning before I was employed by Synteni and ending upon its acquisition by Incyte in early 1998, I understand Synteni was the exclusive licensee of the Stanford-developed cDNA microarray technology, subject to any right that the United States government may have with respect to that technology. In early 1998, I understand Incyte acquired rights under the Stanford-developed cDNA microarray technology as part of its acquisition of Synteni.

I understand that at the time of the commencement of my employment at Synteni in April 1996, Synteni's rights with respect to the Stanford-developed cDNA technology included rights under a United States patent application that had been filed June 7, 1995 in the names of Drs. Brown and Shalon and that subsequently issued as United States Patent No. 5,807,522 (the Brown '522 patent). In December 1995, the subject matter of the Brown '522 patent was published based on a PCT patent application that had also been filed in June 1995. The Brown '522 patent (and its corresponding PCT application) describes the use of the Stanford-developed cDNA technology in a number of gene expression monitoring applications, as will be discussed more fully below.

Upon Incyte's acquisition of Synteni, I became employed by Incyte. From early 1998 until late 1999, I was an Associate Research Director at Incyte. In late 1999, I was promoted to the position of Director, Corporate Development.

I have been aware of the Stanford-developed cDNA microarray technology since shortly before I commenced my employment at Synteni. While I was employed by Synteni, virtually all (if not all) of my work efforts (as well as the work efforts of others employed by Synteni) were directed to the further development and commercial exploitation of that cDNA microarray technology. By the end of 1997, those efforts had progressed to the point that I understand Incyte agreed to pay at least about \$80 million to acquire Synteni. Since I have been employed by Incyte, I have continued to work

on the further development and commercial exploitation of the cDNA microarray technology that was first developed at Stanford in the early to mid-1990s.

3. I have reviewed the specification of a United States patent application that I understand was filed on December 11, 2001 in the names of Yue et al. and was assigned Serial No. 10/018,170 (hereinafter "the Yue '170 application"). Furthermore, I understand that this United States patent application claimed priority to United States Provisional Patent Application Serial No. 60/139,566 filed on June 16, 1999 (hereinafter "the Yue '566 application"). The SEQ ID NO:12-encoding polynucleotides were described in the Yue '566 application. (Note that the sequences of SEQ ID NO:12 and SEQ ID NO:64 disclosed in the Yue '170 application are identical to the sequences referred to as SEQ ID NO:12 and SEQ ID NO:31, respectively, in the Yue '566 application). My remarks herein will therefore be directed to the Yue '566 patent application, and June 16, 1999, as the relevant date of filing. In broad overview, the Yue '566 specification pertains to certain nucleotide and amino acid sequences and their use in a number of applications, including gene expression monitoring applications that are useful in connection with (a) developing drugs (e.g., the diagnosis of inherited and acquired genetic disorders, expression profiling, toxicology testing, and drug development with respect to cancer, an immunopathology, a neuropathology, and the like), and (b) monitoring the activity of drugs for purposes relating to evaluating their efficacy and toxicity.

4. I understand that (a) the Yue '566 application contains claims that are directed to isolated and purified polynucleotides having the sequences disclosed in the Yue '170 application as SEQ ID NO:12-encoding polynucleotides, for example SEQ ID NO:64 (hereinafter "the SEQ ID NO:12-encoding polynucleotides"), and (b) the Patent Examiner has rejected those claims on the grounds that the specification of the Yue '566 application does not disclose a substantial, specific and credible utility for the claimed SEQ ID NO:12-encoding polynucleotides. I further understand that whether or not a patent specification discloses a substantial, specific and credible utility for its claimed subject matter is properly determined from the perspective of a person skilled in the art to which the specification pertains at the time of the patent application was filed. In addition, I understand that a substantial, specific and credible utility under the patent laws must be a "real-world" utility.

5. I have been asked (a) to consider with a view to reaching a conclusion (or conclusions) as to whether or not I agree with the Patent Examiner's position that the Yue '566 application does not disclose a substantial, specific and credible "real-world" utility for the claimed SEQ ID NO:12-encoding polynucleotides, and (b) to state and explain the bases for any conclusions I reach. I have been informed that, in connection with my considerations, I should determine whether or not a person skilled in the art to which the Yue '566 application pertains on June 16, 1999 would have concluded that the Yue '566 application disclosed, for the benefit of the public, a specific beneficial use of the SEQ ID NO:12-encoding polynucleotides in their then available and disclosed form. I have also been informed that, with respect to the "real-world" utility requirement, the Patent and Trademark Office instructs its Patent Examiners in Section 2107 of the Manual of Patent Examining Procedure, under the heading "I. 'Real-World Value' Requirement":

"Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact 'useful' in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified utility and inventions whose specific utility requires further research to identify or reasonably confirm."

6. I have considered the matters set forth in paragraph 5 of this Declaration and have concluded that, contrary to the position I understand the Patent Examiner has taken, the specification of the Yue '566 patent application disclosed to a person skilled in the art at the time of its filing a number of substantial, specific and credible real-world utilities for the claimed SEQ ID NO:12-encoding polynucleotides. More specifically, persons skilled in the art on June 16, 1999 would have understood the Yue '566 application to disclose the use of the SEQ ID NO:12-encoding polynucleotides in a number of gene expression monitoring applications that were well-known at that time to be useful in connection with the development of drugs and the monitoring of the activity of such drugs. I explain the bases for reaching my conclusion in this regard in paragraphs 7-16 below.

7. In reaching the conclusion stated in paragraph 6 of this Declaration, I considered (a) the specification of the Yue '566 application, and (b) a number of published articles and patent documents that evidence gene expression monitoring techniques that were well-known before the June 16, 1999 filing date of the Yue '566 application. The published articles and patent documents I considered are:

- (a) Schena, M., Shalon, D., Heller, R., Chai, A., Brown, P.O., and Davis, R.W., Parallel human genome analysis: Microarray-based expression monitoring of 1000 genes, Proc. Natl. Acad. Sci. USA, 93, 10614-10619 (1996) (hereinafter "the Schena 1996 article") (copy annexed at Tab A);
- (b) Schena, M., Shalon, D., Davis, R.W., Brown, P.O., Quantitative Monitoring of Gene Expression Patterns with a Complementary DNA Microarray, Science, 270, 467-470 (1995) (hereinafter "the Schena 1995 article") (copy annexed at Tab B);
- (c) Shalon and Brown PCT patent application WO 95/35505 titled "Method and Apparatus For Fabricating Microarrays Of Biological Samples," filed on June 16, 1995, and published on December 28, 1995 (hereinafter "the Shalon PCT application") (copy annexed at Tab C);
- (d) Brown and Shalon U.S. Patent No. 5,807,522, corresponding to the Shalon PCT application, titled "Methods For Fabricating Microarrays Of Biological Samples," filed on June 7, 1995 and issued on September 15, 1998 (hereinafter "the Brown '522 patent") (copy annexed at Tab D);
- (e) DeRisi, J., Penland, L., and Brown, P.O. (Group 1); Bittner, M.L., Meltzer, P.S., Ray, M., Chen, Y., Su, Y.A., and Trent, J.M. (Group 2), Use of a cDNA microarray to analyse gene expression patterns in human cancer, Nat. Genet., 14(4), 457-460 (1996) (hereinafter "the DeRisi article") (copy annexed at Tab E);
- (f) Shalon, D., Smith, S.J., and Brown, P.O., A DNA Microarray System for Analyzing Complex DNA Samples Using Two-color Fluorescent Probe Hybridization, Genome Res., 6(7), 639-645 (1996) (hereinafter "the Shalon article") (copy annexed at Tab F);
- (g) Heller, R.A., Schena, M., Chai A., Shalon, D., Bedilion, T., Gilmore, J., Woolley, D.E., and Davis R.W., Discovery and analysis of inflammatory disease-related genes using

cDNA microarrays, Proc. Natl. Acad. Sci. USA, 94, 2150-2155 (1997) (hereinafter “the Heller article”)(copy annexed at Tab G);

(h) Sambrook, J., Fritsch, E.F., Maniatis, T., Molecular Cloning, A Laboratory Manual, pages 7.37 and 7.38, Cold Spring Harbor Press (1989) (hereinafter “the Sambrook Manual”) (copy annexed at Tab H);

8. Many of the published articles and patent documents I considered (i.e., at least items (a)-(g) identified in paragraph 7) relate to work done at Stanford University in the early and mid-1990s with respect to the development of cDNA microarrays for use in gene expression monitoring applications under which Synteni became exclusively licensed. As I will discuss, a person skilled in the art who read the Yue ‘566 application on June 16, 1999 would have understood that application to disclose the SEQ ID NO:12-encoding polynucleotides to be useful for a number of gene expression monitoring applications, e.g., as a probe for the expression of that specific polynucleotide in cDNA microarrays of the type first developed at Stanford.

9. Turning more specifically to the Yue ‘566 specification, the SEQ ID NO:64 polynucleotide (referred to as SEQ ID NO:31 in the Yue ‘566 application) is shown at p. 33 as one of 38 sequences under the heading “Sequence Listing.” The Yue ‘566 specification specifically teaches that the invention provides isolated and purified polynucleotides that encode INSIG (Yue ‘566 application at p. 3). It further teaches that (a) the identity of the SEQ ID NO:64 polynucleotide was determined from a diseased gallbladder tissue cDNA library (GBLANOT01) (Yue ‘566 application, Table 4), (b) the SEQ ID NO:64 polynucleotide encodes for the annexin protein (INSIG) shown as SEQ ID NO:12 (Yue ‘566 application at Tables 1 and 2), and (c) northern analysis of SEQ ID NO:64 shows its expression predominantly in cDNA libraries associated with reproductive, gastrointestinal, and nervous system tissues and in tissues associated with cancer and inflammation (Yue ‘566 application at Table 4).

The Yue ‘566 application discusses a number of uses of the SEQ ID NO:12-encoding polynucleotides in addition to their use in gene expression monitoring applications. I have not fully evaluated these additional uses in connection with the preparation of this Declaration and do not express any views in this Declaration regarding whether or not the Yue ‘566 specification discloses

these additional uses to be substantial, specific and credible real-world utilities of the SEQ ID NO:12-encoding polynucleotides. Consequently, my discussion in this Declaration concerning the Yue '566 application focuses on the portions of the application that relate to the use of the SEQ ID NO:12-encoding polynucleotides in gene expression monitoring applications.

10. The Yue '566 application discloses that the polynucleotide sequences disclosed therein, including the SEQ ID NO:12-encoding polynucleotides, are useful as probes in microarrays. It further teaches that the microarrays can be used "to monitor the expression level of large numbers of genes simultaneously" for a number of purposes, including "to develop and monitor the activities of therapeutic agents" (Yue '566 application at p. 34, lines 10-15).

In the paragraph immediately following the Yue '566 teachings described in the preceding paragraph of this Declaration, the Yue '566 application teaches that microarrays can be prepared using the previously mentioned cDNA microarray technology developed at Stanford in the early to mid-1990s. In this connection, the Yue '566 application specifically cites to the Schena 1996 article identified in item (a) of paragraph 7 of this Declaration (Yue '566 application at p. 34; *supra*, paragraph 7).

The Schena 1996 article is one of a number of documents that were published prior to the June 16, 1999 filing date of the Yue '566 application that describes the use of the Stanford-developed cDNA technology in a wide range of gene expression monitoring applications, including monitoring and analyzing gene expression patterns in human cancer. In view of the Yue '566 application, the Schena 1996 article, and other related pre-June, 1999 publications, persons skilled in the art on June 16, 1999 clearly would have understood the Yue '566 application to disclose the SEQ ID NO:12-encoding polynucleotides to be useful in cDNA microarrays for the development of new drugs and monitoring the activities of drugs for such purposes as evaluating their efficacy and toxicity, as explained more fully in paragraph 15 below.

With specific reference to toxicity evaluations, those of skill in the art who were working on drug development in June, 1999 (and for many years prior to June, 1999) without any doubt appreciated that the toxicity (or lack of toxicity) of any proposed drug they were working on was one of the most important criteria to be considered and evaluated in connection with the development

of the drug. They would have understood at that time that good drugs are not only potent, they are specific. This means that they have strong effects on a specific biological target and minimal effects on all other biological targets. Ascertaining that a candidate drug affects its intended target, and identification of undesirable secondary effects (i.e., toxic side effects), had been for many years among the main challenges in developing new drugs. The ability to determine which genes are positively affected by a given drug, coupled with the ability to quickly and at the earliest time possible in the drug development process identify drugs that are likely to be toxic because of their undesirable secondary effects, have enormous value in improving the efficiency of the drug discovery process, and are an important and essential part of the development of any new drug. Accordingly, the teachings in the Yue '566 application, in particular regarding use of the SEQ ID NO:12-encoding polynucleotides in differential gene expression analysis and in the development and the monitoring of the activities of drugs, clearly includes toxicity studies and persons skilled in the art who read the Yue '566 application on June 16, 1999 would have understood that to be so.

11. The Schena 1996 article was not the first publication that described the use of the cDNA microarray technique developed at Stanford to monitor quantitatively gene expression patterns. More than a year earlier (i.e., in October 1995), the Schena 1995 article, titled "Quantitative Monitoring of Gene Expression Patterns with a Complementary DNA Microarray", was published (see Tabs A and B).

12. As previously discussed (*supra*, paragraphs 2 and 7), in the mid-1990s patent applications were filed in the names of Drs. Shalon and Brown that described the Stanford-developed cDNA microarray technology. The two patent documents (i.e., the Shalon PCT application and the Brown '522 patent) annexed to this Declaration at Tabs C and D evidence information that was available to the public regarding the Stanford-developed cDNA microarray technology before the June 16, 1999 filing date of the Yue '566 application.

The Shalon PCT patent application, which was published in December 1995, contains virtually the same (if not exactly the same) specification as the Brown '522 patent. Hence, the Brown '522 patent disclosure was, in effect, available to the public as of the December 1995 publication date

of the Shalon PCT application(see Tabs C and D). For the sake of convenience, I cite to and discuss the Brown '522 specification below on the understanding that the descriptions in that specification were published as of the December 28, 1995 publication date of the Shalon PCT application.

The Brown '522 patent discusses, in detail, the utility of the Stanford-developed cDNA microarrays in gene expression monitoring applications. For example, in the "Summary Of The Invention" section, the Brown '522 patent teaches (see Tab D, col. 4, line 52-col. 5, line 8):

Also forming part of the invention is a method of detecting differential expression of each of a plurality of genes in a first cell type, with respect to expression of the same genes in a second cell type. In practicing the method, there is first produced fluorescent-labeled cDNAs from mRNAs isolated from two cells types, where the cDNAs from the first and second cell types are labeled with first and second different fluorescent reporters.

A mixture of the labeled cDNAs from the two cell types is added to an array of polynucleotides representing a plurality of known genes derived from the two cell types, under conditions that result in hybridization of the cDNAs to complementary-sequence polynucleotides in the array. The array is then examined by fluorescence under fluorescence excitation conditions in which (i) polynucleotides in the array that are hybridized predominantly to cDNAs derived from one of the first or second cell types give a distinct first and second fluorescence emission color, respectively, and (ii) polynucleotides in the array that are hybridized to substantially equal numbers of cDNAs derived from the first and second cell types give a distinct combined fluorescence emission color, respectively. The relative expression of known genes in the two cell types can then be determined by the observed fluorescence emission color of each spot.

The Brown '522 patent further teaches that the "[m]icroarrays of immobilized nucleic acid sequences prepared in accordance with the invention" can be used in "numerous" genetic applications, including "monitoring of gene expression" applications (see Tab D at col. 14, lines 36-42). The Brown '522 patent teaches (a) monitoring gene expression (i) in different tissue types, (ii) in different disease states, and (iii) in response to different drugs, and (b) that arrays disclosed therein may be used in toxicology studies (see Tab D at col. 15, lines 13-18 and 52-58 and col. 18, lines 25-30).

13. Also pertinent to my considerations underlying this Declaration is the DeRisi article, published in December 1996. The DeRisi article describes the use of the Stanford-developed cDNA microarray technology "to analyze gene expression patterns in human cancer" (see Tab E at, e.g., p. 457). The DeRisi article specifically indicates, consistent with what was apparent to persons skilled in the art in December 1996, that increasing the number of genes on the cDNA microarray permits a "more comprehensive survey of gene expression patterns," thereby enhancing the ability of the cDNA microarray to provide "new and useful insights into human biology and a deeper understanding of the gene pathways involved in the pathogenesis of cancer and other diseases" (see Tab E at p. 458).

14. Other pre-June, 1999 publications further evidence the utility of the cDNA microarrays first developed at Stanford in a wide range of gene expression monitoring applications (see, e.g., the Shalon and the Heller articles at Tabs F and G). By no later than the March 1997 publication of the Heller article, these publications showed that employees of Synteni (i.e., James Gilmore and myself) had used the cDNA microarrays in specific gene expression monitoring applications (see Tab G).

The Heller article states that the results reported therein "successfully demonstrate the use of the cDNA microarray system as a general approach for dissecting human diseases" (Tab G at p. 2150). Among other things, the Heller article describes the investigation of "1000 human genes that were randomly selected from a peripheral human blood cell library" and "[t]heir differential and quantitative expression analysis in cells of the joint tissue. . . to demonstrate the utility of the microarray method to analyze complex diseases by their pattern of gene expression" (see Tab G at pp. 2150 *et seq.*).

Much of the work reported on in the Heller article was done in 1996. That article, therefore, evidences how persons skilled in the art were readily able, well prior to June 16, 1999, to make and use cDNA microarrays to achieve highly useful results. For example, as reported in the Heller article, a cDNA microarray that was used in some of the highly successful work reported on therein was made from 1,000 genes randomly selected from a human blood cell library.

15. A person skilled in the art on June 16, 1999, who read the Yue '566 application, would understand that application to disclose the SEQ ID NO:12-encoding polynucleotides, for example, SEQ ID NO:64, to be highly useful as probes for the expression of that specific polynucleotide in cDNA microarrays of the type first developed at Stanford. For example, the specification of the Yue '566 application would have led a person skilled in the art in June, 1999 who was using gene expression monitoring in connection with working on developing new drugs for the treatment of cancer, immune disorders, neurological disorders, and gastrointestinal disorders to conclude that a cDNA microarray that contained the SEQ ID NO:12-encoding polynucleotides would be a highly useful tool and to request specifically that any cDNA microarray that was being used for such purposes contain the SEQ ID NO:12-encoding polynucleotides. Persons skilled in the art would appreciate that cDNA microarrays that contained the SEQ ID NO:12-encoding polynucleotides would be a more useful tool than cDNA microarrays that did not contain the polynucleotides in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating cancer, immune disorders, neurological disorders, and gastrointestinal disorders for such purposes as evaluating their efficacy and toxicity.

I discuss in more detail in items (a)-(g) below a number of reasons why a person skilled in the art, who read the Yue '566 specification in June, 1999, would have concluded based on that specification and the state of the art at that time, that the SEQ ID NO:12-encoding polynucleotides would be a highly useful tool for inclusion in cDNA microarrays for evaluating the efficacy and toxicity of proposed drugs for treating cancer, immune disorders, neurological disorders, and gastrointestinal disorders, as well as for other evaluations:

(a) The Yue '566 application teaches the SEQ ID NO:12-encoding polynucleotides to be useful as probes in cDNA microarrays of the type first developed at Stanford. It also teaches that such cDNA microarrays are useful in a number of gene expression monitoring applications, including "developing and monitoring the activity of therapeutic agents [i.e., drugs]" (see paragraph 10, *supra*).

(b) By June, 1999, the Stanford-developed cDNA microarray technology was a well known and widely accepted tool for use in a wide range of gene expression monitoring applications. This is evidenced, for example, by numerous publications describing the use of that

cDNA technology in gene expression monitoring applications and the fact that, for over a year, the technology had provided the basis for the operations of an up-and-running company (Synteni), with employees, that was created for the purpose of developing and commercially exploiting that technology (see paragraphs 2, 8 and 10-14, *supra*). The fact that Incyte agreed to purchase Synteni in late 1997 for an amount reported to be at least about \$80 million only serves to underscore the substantial practical and commercial significance, in 1997, of the cDNA microarray technology first developed at Stanford (see paragraph 2, *supra*).

(c) The pre-June, 1999 publications regarding the cDNA microarray technology first developed at Stanford that I discuss in this Declaration repeatedly confirm that, consistent with the teachings in the Yue '566 application, cDNA microarrays are highly useful tools for conducting gene expression monitoring applications with respect to the development of drugs and the monitoring of their activity. Among other things, those pre-June, 1999 publications confirmed that cDNA microarrays (i) were useful for monitoring gene expression responses to different drugs (see paragraph 12, *supra*), (ii) were useful in analyzing gene expression patterns in human cancer, with increasing the number of genes on the cDNA microarray enhancing the ability of the cDNA microarray to provide useful information (see paragraph 13, *supra*), and (iii) were a valuable tool for use as part of a "general approach for dissecting human diseases" and for "anayl[ing] complex diseases by their pattern of gene expression" (see paragraph 14, *supra*).

(d) Based on my own extensive work for a company whose business was the development and commercial exploitation of cDNA microarray technology for more than two years prior to the June, 1999 filing date of the Yue '566 application, I have first-hand knowledge concerning the state of the art with respect to making and using cDNA microarrays as of June 16, 1999 (see paragraphs 2 and 14, *supra*). Persons skilled in the art as of that date would have (a) concluded that the Yue '566 application disclosed cDNA microarrays containing the SEQ ID NO:12-encoding polynucleotides to be useful, and (b) readily been able to make and use such microarrays with useful results.

(e) The Yue '566 specification contains a number of teachings that would lead persons skilled in the art on June 16, 1999 to conclude that a cDNA microarray that contained the SEQ ID NO:12-encoding polynucleotides would be a more useful tool for gene expression monitoring

applications relating to drugs for treating cancer, immune disorders, neurological disorders, and gastrointestinal disorders than a cDNA microarray that did not contain the SEQ ID NO:12-encoding polynucleotides. Among other things, the Yue '566 specification teaches that the identity of the SEQ ID NO:64 polynucleotide was determined from a diseased gallbladder cDNA library (GBLANOT01) (Yue '566 application, Table 4). Moreover, northern analysis of SEQ ID NO:64 shows its expression predominantly in cDNA libraries associated with reproductive, gastrointestinal, and nervous system tissues and in tissues associated with cancer and inflammation. (Yue '566 application at Table 3). (See paragraph 9, *supra*).

Moreover, the Yue '566 specification teaches that the INSIG protein having the amino acid sequence of SEQ ID NO:12 shares homology with known functional proteins. INSIG-12 is a member of the annexin protein family. In particular, SEQ ID NO:12 shares homology with the sequence of the non-CD4 glycoprotein gp120 receptor (GENESEQ AAR32188). (Yue '566 application, at Table 2).

(f) Persons skilled in the art on June 16, 1999 would have appreciated (i) that the gene expression monitoring results obtained using a cDNA microarray containing a probe to a sequence selected from the group consisting of SEQ ID NO:12-encoding polynucleotides would vary, depending on the particular drug being evaluated, and (ii) that such varying results would occur both with respect to the results obtained from the probe described in (i) and from the cDNA microarray as a whole (including all its other individual probes). These kinds of varying results, depending on the identity of the drug being tested, in no way detracts from my conclusion that persons skilled in the art on June 16, 1999, having read the Yue '566 specification, would specifically request that any cDNA microarray that was being used for conducting gene expression monitoring studies on drugs for treating cancer, immune disorders, neurological disorders, and gastrointestinal disorders (e.g., a toxicology study or any efficacy study of the type that typically takes place in connection with the development of a drug) contain any one of the SEQ ID NO:12-encoding polynucleotides as a probe. Persons skilled in the art on June 16, 1999 would have wanted their cDNA microarray to have a probe as described in (i) because a microarray that contained such a probe (as compared to one that did not) would provide more useful results in the kind of gene expression monitoring studies using cDNA microarrays that persons skilled in the art have been doing since well prior to June 16, 1999.

The foregoing is not intended to be an all-inclusive explanation of all my reasons for reaching the conclusions stated in this paragraph 15, and in paragraph 6, *supra*. In my view, however, it provides more than sufficient reasons to justify my conclusions stated in paragraph 6 of this Declaration regarding the Yue '566 application disclosing to persons skilled in the art at the time of its filing substantial, specific and credible real-world utilities for the SEQ ID NO:12-encoding polynucleotides.

16. Also pertinent to my considerations underlying this Declaration is the fact that the Yue '566 disclosure regarding the uses of the SEQ ID NO:64 polynucleotide for gene expression monitoring applications is not limited to the use of that polynucleotide as a probe in microarrays. For one thing, the Yue '566 disclosure regarding the hybridization technique used in gene expression monitoring applications is broad (Yue '566 application at, e.g., p. 4, lines 2-8).

In addition, the Yue '566 specification repeatedly teaches that the polynucleotides described therein (including the polynucleotide of SEQ ID NO:64) may desirably be used as probes in any of a number of long established "standard" non-microarray techniques, such as Northern analysis, for conducting gene expression monitoring studies. See, e.g.:

- (a) Yue '566 application at p. 8, lines 21-24 ("[N]orthern analysis is indicative of the presence of nucleic acids encoding INSIG in a sample, and thereby correlates with expression of the transcript from the polynucleotide encoding INSIG");
- (b) Yue '566 application at p. 32, line 35 through p. 33, line 3 ("The polynucleotide sequences encoding INSIG may be used in Southern or northern analysis, dot blot, or other membrane-based technologies; in PCR technologies; in dipstick, pin, and multiformat ELISA-like assays; and in microarrays utilizing fluids or tissues from patients to detect altered INSIG expression. Such qualitative or quantitative methods are well known in the art");
- (c) Yue '566 application at p. 33, lines 14-22 ("In order to provide a basis for the diagnosis of a disorder associated with expression of INSIG, a normal or standard profile for expression is established. This may be accomplished by combining body fluids or cell extracts taken from normal subjects, either animal or human, with a sequence, or a fragment thereof, encoding INSIG, under conditions suitable for hybridization or amplification. Standard hybridization may be quantified by

comparing the values obtained from normal subjects with values from an experiment in which a known amount of a substantially purified polynucleotide is used. Standard values obtained in this manner may be compared with values obtained from samples from patients who are symptomatic for a disorder.

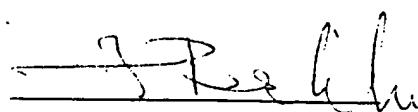
Deviation from standard values is used to establish the presence of a disorder"); and

(d) Yue '566 application at p. 38, lines 14-18 ("Northern analysis is a laboratory technique used to detect the presence of a transcript of a gene and involves the hybridization of a labeled nucleotide sequence to a membrane on which RNAs from a particular cell type or tissue have been bound. (See, e.g., Sambrook, supra, ch. 7; Ausubel, 1995, supra, ch. 4 and 16.)").

The "Sambrook et al." reference cited in item (d) immediately above is a reference that was well known to persons skilled in the art in June, 1999. A copy of pages from that reference manual, which was published in 1989, is annexed to this Declaration at Tab H. The attached pages from the Sambrook manual provide an overview of northern analysis and other membrane-based technologies for conducting gene expression monitoring studies that were known and used by persons skilled in the art for many years prior to the June 16, 1999 filing date of the Yue '566 application.

A person skilled in the art on June 16, 1999, who read the Yue '566 specification, would have routinely and readily appreciated that the SEQ ID NO:12-encoding polynucleotides disclosed therein would be useful as a probe to conduct gene expression monitoring analyses using northern analysis or any of the other traditional membrane-based gene expression monitoring techniques that were known and in common use many years prior to the filing of the Yue '566 application. For example, a person skilled in the art in June, 1999 would have routinely and readily appreciated that the SEQ ID NO:12-encoding polynucleotides would be a useful tool in conducting gene expression analyses, using the northern analysis technique, in furtherance of (a) the development of drugs for the treatment of cancer, immune disorders, neurological disorders, and gastrointestinal disorders, and (b) analyses of the efficacy and toxicity of such drugs.

17. I declare further that all statements made herein of my own knowledge are true and that all statements made herein on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, and that willful false statements may jeopardize the validity of this application and any patent issuing thereon.



Tod Bedilion

Signed at Redwood City, California

this 21<sup>st</sup> day of April, 2003

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: [Mail Stop: Non-Fee Amendment], Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on \_\_\_\_\_

August 27, 2003

By: KPS

Printed: Katherine Sofer

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of: Yue et al.

Title: INTRACELLULAR SIGNALING MOLECULES

Serial No.: 10/018,170 Filing Date: December 11, 2001

Examiner: Steadman, D Group Art Unit: 1652

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Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

**DECLARATION OF LARS MICHAEL FURNESS**  
**UNDER 37 C.F.R. § 1.132**

I, L. MICHAEL FURNESS, a citizen of the United Kingdom, residing at 2 Brookside, Exning, Newmarket, United Kingdom, declare that:

1. I was employed by Incyte Genomics, Inc. (hereinafter "Incyte") as a Director of Pharmacogenomics until December 31, 2001. I am currently under contract to be a Consultant to Incyte Genomics, Inc.

2. In 1984, I received a B.Sc.(Hons) in Biomolecular Science (Biophysics and Biochemistry) from Portsmouth Polytechnic.

From 1985-1987 I was at the School of Pharmacy in London, United Kingdom, during which time I analyzed lipid methyltransferase enzymes using a variety of protein analysis methods, including one-dimensional (1D) and two-dimensional (2D) gel electrophoresis, HPLC, and a variety of enzymatic assay systems.

I then worked in the Protein Structure group at the National Institute for Medical Research until 1989, setting up core facilities for nucleic acid synthesis and sequencing, as well as assisting in programs on protein kinase C inhibitors.

After a year at Perkin Elmer-Applied Biosystems as a technical specialist, I worked at the Imperial Cancer Research Fund between 1990-1992, on a Eureka-funded program collaborating with Amersham Pharmacia in the United Kingdom and CEPH (Centre d'Etude du Polymorphisme Humaine) in Paris, France, to develop novel nucleic acid purification and characterization methods.

In 1992, I moved to Pfizer Central Research in the United Kingdom, where I stayed until 1998, initially setting up core DNA sequencing and then a DNA arraying facility for gene expression analysis in 1993. My work also included bioinformatics and I was responsible for the support of all Pfizer neuroscience programs in the United Kingdom. This then led me into carrying out detailed bioinformatics and wet lab work on the sodium channels, including antibody generation, Western and Northern analyses, PCR, tissue distribution studies, and sequence analyses on novel sequences identified.

In 1998, I moved to Incyte Genomics, Inc., to the Pharmacogenomics group to look at the application of genomics and proteomics to the pharmaceutical industry. In 1999, I was appointed director of the LifeExpress Lead Program which used microarray and protein expression data to identify pharmacologically and toxicologically relevant mechanisms to assist in improved drug design and development.

On December 12, 2001 I founded Nuomics Consulting Ltd., in Exning, U.K., and I am currently employed as Managing Director. Nuomics Consulting Ltd. will be providing expert technical knowledge and advice to businesses around the areas of genomics, proteomics, pharmacogenomics, toxicogenomics and chemogenomics.

3. I have reviewed the specification of a United States patent application that I understand was filed on December 11, 2001 in the names of Yue et al. and was assigned Serial No. 10/018,170 (hereinafter "the Yue '170 application"). Furthermore, I understand that this United States patent application claimed priority to United States Provisional Patent Application Serial No.

60/139,566 filed on June 16, 1999 (hereinafter "the Yue '566 application"). The SEQ ID NO:12-encoding polynucleotides were described in the Yue '566 application. (Note that the sequences of SEQ ID NO:12 and SEQ ID NO:64 disclosed in the Yue '170 application are identical to the sequences referred to as SEQ ID NO:12 and SEQ ID NO:31, respectively, in the Yue '566 application). My remarks herein will therefore be directed to the Yue '566 patent application, and June 16, 1999, as the relevant date of filing. In broad overview, the Yue '566 specification pertains to certain nucleotide and amino acid sequences and their use in a number of applications, including gene and protein expression monitoring applications that are useful in connection with (a) developing drugs (e.g., for the treatment of cancer), and (b) monitoring the activity of drugs for purposes relating to evaluating their efficacy and toxicity.

4. I understand that (a) the Yue '170 application contains claims that are directed to a substantially purified polypeptide having the sequence disclosed in the Yue '170 application as SEQ ID NO:12 (hereinafter "the SEQ ID NO:12 polypeptide"), and (b) the Patent Examiner has rejected those claims on the grounds that the specification of the Yue '170 application does not disclose a substantial, specific and credible utility for the claimed SEQ ID NO:12 polypeptide. I further understand that whether or not a patent specification discloses a substantial, specific and credible utility for its claimed subject matter is properly determined from the perspective of a person skilled in the art to which the specification pertains at the time of the patent application was filed. In addition, I understand that a substantial, specific and credible utility under the patent laws must be a "real-world" utility.

5. I have been asked (a) to consider with a view to reaching a conclusion (or conclusions) as to whether or not I agree with the Patent Examiner's position that the Yue '170 application and its parent, the Yue '566 application, does not disclose a substantial, specific and credible "real-world" utility for the claimed SEQ ID NO:12 polypeptide, and (b) to state and explain the bases for any conclusions I reach. I have been informed that, in connection with my considerations, I should determine whether or not a person skilled in the art to which the Yue '566 application pertains

on June 16, 1999, would have concluded that the '566 application disclosed, for the benefit of the public, a specific beneficial use of the SEQ ID NO:12 polypeptide in its then available and disclosed form. I have also been informed that, with respect to the "real-world" utility requirement, the Patent and Trademark Office instructs its Patent Examiners in Section 2107 of the Manual of Patent Examining Procedure, under the heading 'I. 'Real-World Value' Requirement':

"Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact 'useful' in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified utility and inventions whose specific utility requires further research to identify or reasonably confirm."

6. I have considered the matters set forth in paragraph 5 of this Declaration and have concluded that, contrary to the position I understand the Patent Examiner has taken, the specification of the Yue '566 patent application disclosed to a person skilled in the art at the time of its filing a number of substantial, specific and credible real-world utilities for the claimed SEQ ID NO:12 polypeptide. More specifically, persons skilled in the art on June 16, 1999 would have understood the Yue '566 application to disclose the use of the SEQ ID NO:12 polypeptide as a research tool in a number of gene and protein expression monitoring applications that were well-known at that time to be useful in connection with the development of drugs and the monitoring of the activity of such drugs. I explain the bases for reaching my conclusion in this regard in paragraphs 7-13 below.

7. In reaching the conclusion stated in paragraph 6 of this Declaration, I considered (a) the specification of the Yue '566 application, and (b) a number of published articles and patent documents that evidence gene and protein expression monitoring techniques that were well-known before the June 16, 1999 filing date of the Yue '566 application. The published articles and patent documents I considered are:

(a) Anderson, N.L., Esquer-Blasco, R., Hofmann, J.-P., Anderson, N.G., A Two-Dimensional Gel Database of Rat Liver Proteins Useful in Gene Regulation and Drug Effects Studies, Electrophoresis, 12, 907-930 (1991) (hereinafter "the Anderson 1991 article") (copy annexed at Tab A);

(b) Anderson, N.L., Esquer-Blasco, R., Hofmann, J.-P., Mehues, L., Raymackers, J., Steiner, S. Witzmann, F., Anderson, N.G., An Updated Two-Dimensional Gel Database of Rat Liver Proteins Useful in Gene Regulation and Drug Effect Studies, Electrophoresis, 16, 1977-1981 (1995) (hereinafter "the Anderson 1995 article") (copy annexed at Tab B);

(c) Wilkins, M.R., Sanchez, J.-C., Gooley, A.A., Appel, R.D., Humphery-Smith, I., Hochstrasser, D.F., Williams, K.L., Progress with Proteome Projects: Why all Proteins Expressed by a Genome Should be Identified and How To Do It, Biotechnology and Genetic Engineering Reviews, 13, 19-50 (1995) (hereinafter "the Wilkins article") (copy annexed at Tab C);

(d) Celis, J.E., Rasmussen, H.H., Leffers, H., Madsen, P., Honore, B., Gesser, B., Dejgaard, K., Vandekerckhove, J., Human Cellular Protein Patterns and their Link to Genome DNA Sequence Data: Usefulness of Two-Dimensional Gel Electrophoresis and Microsequencing, FASEB Journal, 5, 2200-2208 (1991) (hereinafter "the Celis article") (copy annexed at Tab D);

(e) Franzen, B., Linder, S., Okuzawa, K., Kato, H., Auer, G., Nonenzymatic Extraction of Cells from Clinical Tumor Material for Analysis of Gene Expression by Two-Dimensional Polyacrylamide Gel Electrophoresis, Electrophoresis, 14, 1045-1053 (1993) (hereinafter "the Franzen article") (copy annexed at Tab E);

(f) Bjellqvist, B., Basse, B., Olsen, E., Celis, J.E., Reference Points for Comparisons of Two-Dimensional Maps of Proteins from Different Human Cell Types Defined in a pH Scale Where Isoelectric Points Correlate with Polypeptide Compositions, Electrophoresis, 15, 529-539 (1994) (hereinafter "the Bjellqvist article") (copy annexed at Tab F);

(g) Large Scale Biology Company Info; LSB and LSP Information; from <http://www.lsbc.com> (2001) (copy annexed at Tab G);

8. Many of the published articles I considered (i.e., at least items (a)-(f) identified in paragraph 7) relate to the development of protein two-dimensional gel electrophoretic techniques for use in protein expression monitoring applications in drug development and toxicology. As I will discuss below, a person skilled in the art who read the Yue '566 application on June 16, 1999 would have understood that application to disclose the SEQ ID NO:12 polypeptide to be useful for a number of protein expression monitoring applications, e.g., in the use of two-dimensional polyacrylamide gel electrophoresis and western blot analysis of tissue samples in drug development and in toxicity testing.

Furthermore, items (a)-(f) establish that protein two-dimensional polyacrylamide gel electrophoresis and western blot analysis were well-known and established methods routinely used in toxicology testing and drug development at the time of filing the Yue '566 application and for several years prior to June 16, 1999. As such, one of ordinary skill in the art would have recognized that the polypeptide of SEQ ID NO:12 could be used in toxicology testing and drug development, irrespective of its biochemical activities.

9. Turning more specifically to the Yue '566 specification, the SEQ ID NO:12 polypeptide is shown at pages 14-15 as one of 38 sequences under the heading "Sequence Listing." The Yue '566 specification specifically teaches that the invention features a "substantially purified" polypeptide, human annexin (INSIG-12) having the amino acid sequence shown in SEQ ID NO:12" (Yue '566 application at p. 3 and Table 2). It further teaches that (a) the identity of the SEQ ID NO:12 polypeptide was determined from a diseased gallbladder tissue cDNA library (GBLANOT01) (Yue '566 application, Table 4), (b) the SEQ ID NO:12 polypeptide is the annexin referred to as "INSIG-12" and is encoded by SEQ ID NO:64, and (c) northern analysis shows that "INSIG-12 is expressed predominantly in cDNA libraries associated with reproductive, gastrointestinal, and nervous system tissues and in tissues associated with cancer and inflammation (Yue '566 application at Table 3).

The Yue '566 application discusses a number of uses of the SEQ ID NO:12 polypeptide in addition to its use in protein expression monitoring applications. I have not fully evaluated these additional uses in connection with the preparation of this Declaration and do not

express any views in this Declaration regarding whether or not the Yue '566 specification discloses these additional uses to be substantial, specific and credible real-world utilities of the SEQ ID NO:12 polypeptide. Consequently, my discussion in this Declaration concerning the Yue '566 application focuses on the portions of the application that relate to the use of the SEQ ID NO:12 polypeptide in gene and protein expression monitoring applications.

10. The Yue '566 application discloses that the polynucleotide sequences disclosed therein, including the polynucleotides encoding the SEQ ID NO:12 polypeptide, are useful as probes in chip based technologies. It further teaches that the chip based technologies can be used "for the detection and/or quantification of nucleic acid or protein" (Yue '566 application at p. 20, lines 17-20).

The Yue '566 application also discloses that the SEQ ID NO:12 polypeptide is useful in other protein expression detection technologies. The Yue '566 application states that "[a] methods for detecting and measuring the expression of INSIG using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS)" (Yue '566 application at p. 20, lines 21-24). Furthermore, the Yue '566 application discloses that "[a] variety of protocols for measuring INSIG, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of INSIG expression. Normal or standard values for INSIG expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, preferably human, with antibody to INSIG under conditions suitable for complex formation" (Yue '566 application at p. 31, lines 2-6).

In addition, at the time of filing the Yue '566 application, it was well known in the art that "gene" and protein expression analyses also included two-dimensional polyacrylamide gel electrophoresis (2-D PAGE) technologies, which were developed during the 1980s, and as exemplified by the Anderson 1991 and 1995 articles (Tab A and Tab B). The Anderson 1991 article teaches that a 2-D PAGE map has been used to connect and compare hundreds of 2-D gels of rat liver samples from a variety of studies including regulation of protein expression by various drugs and toxic agents (Tab A at p. 907). The Anderson 1991 article teaches an empirically-determined standard curve fitted

to a series of identified proteins based upon amino acid chain length (Tab A at p. 911) and how that standard curve can be used in protein expression analysis. The Anderson 1991 article teaches that "there is a long-term need for a comprehensive database of liver proteins" (Tab A at p. 912).

The Wilkins article is one of a number of documents that were published prior to the June 16, 1999 filing date of the Yue '566 application that describes the use of the 2-D PAGE technology in a wide range of gene and protein expression monitoring applications, including monitoring and analyzing protein expression patterns in human cancer, human serum plasma proteins, and in rodent liver following exposure to toxins. In view of the Yue '566 application, the Wilkins article, and other related pre-June 1999 publications, persons skilled in the art on June 16, 1999 clearly would have understood the Yue '566 application to disclose the SEQ ID NO:12 polypeptide to be useful in 2-D PAGE analyses for the development of new drugs and monitoring the activities of drugs for such purposes as evaluating their efficacy and toxicity, as explained more fully in paragraph 12 below.

With specific reference to toxicity evaluations, those of skill in the art who were working on drug development in June 1999 (and for many years prior to June 1999) without any doubt appreciated that the toxicity (or lack of toxicity) of any proposed drug they were working on was one of the most important criteria to be considered and evaluated in connection with the development of the drug. They would have understood at that time that good drugs are not only potent, they are specific. This means that they have strong effects on a specific biological target and minimal effects on all other biological targets. Ascertaining that a candidate drug affects its intended target, and identification of undesirable secondary effects (i.e., toxic side effects), had been for many years among the main challenges in developing new drugs. The ability to determine which genes are positively affected by a given drug, coupled with the ability to quickly and at the earliest time possible in the drug development process identify drugs that are likely to be toxic because of their undesirable secondary effects, have enormous value in improving the efficiency of the drug discovery process, and are an important and essential part of the development of any new drug. In fact, the desire to identify and understand toxicological effects using the experimental assays described above led Dr Leigh Anderson to found the Large Scale Biology Corporation in 1985, in order to pursue commercial development of the 2-D electrophoretic protein mapping technology he had developed. In addition, the company focused on

toxicological effects on the proteome as clearly demonstrated by its goals and by its senior management credentials described in company documents (see Tab G at pp. 1, 3, and 5).

Accordingly, the teachings in the Yue '566 application, in particular regarding use of SEQ ID NO:12 in differential gene and protein expression analysis (2-D PAGE maps) and in the development and the monitoring of the activities of drugs, clearly includes toxicity studies and persons skilled in the art who read the Yue '566 application on June 16, 1999 would have understood that to be so.

11. As previously discussed (*supra*, paragraphs 7 and 8), my experience with protein analysis methods in the mid-1980s and the several publications annexed to this Declaration at Tabs A through F evidence information that was available to the public regarding two-dimensional polyacrylamide gel electrophoresis technology and its uses in drug discovery and toxicology testing before the June 16, 1999 filing date of the Yue '566 application. In particular the Celis article stated that "protein databases are expected to foster a variety of biological information.... -- among others, .... drug development and testing" (See Tab D, p. 2200, second column). The Franzen article shows that 2-D PAGE maps were used to identify proteins in clinical tumor material (See Tab E). The Yue '566 application clearly discloses that expression of INSIG is associated with reproductive, gastrointestinal, and nervous system tissues and tissues associated with cancer and inflammation. (Yue '566 application at Table 3). The Bjellqvist article showed that a protein may be identified accurately by its positional co-ordinates, namely molecular mass and isoelectric point (See Tab F). The Yue '566 application clearly disclosed SEQ ID NO:12 from which it would have been routine for one of skill in the art to predict both the molecular mass and the isoelectric point using algorithms well known in the art at the time of filing.

12. A person skilled in the art on June 16, 1999, who read the Yue '566 application, would understand that application to disclose the SEQ ID NO:12 polypeptide to be highly useful in analysis of differential expression of proteins. For example, the specification of the Yue '566 application would have led a person skilled in the art in June 1999 who was using protein expression

monitoring in connection with working on developing new drugs for the treatment of cancer, immune disorders, neurological disorders, and gastrointestinal disorders to conclude that a 2-D PAGE map that used the substantially purified SEQ ID NO:12 polypeptide would be a highly useful tool and to request specifically that any 2-D PAGE map that was being used for such purposes utilize the SEQ ID NO:12 polypeptide sequence. Expressed proteins are useful for 2-D PAGE analysis in toxicology expression studies for a variety of reasons, particularly for purposes relating to providing controls for the 2-D PAGE analysis, and for identifying sequence or post-translational variants of the expressed sequences in response to exogenous compounds. Persons skilled in the art would appreciate that a 2-D PAGE map that utilized the SEQ ID NO:12 polypeptide sequence would be a more useful tool than a 2-D PAGE map that did not utilize this protein sequence in connection with conducting protein expression monitoring studies on proposed (or actual) drugs for treating cancer, immune disorders, neurological disorders, and gastrointestinal disorders for such purposes as evaluating their efficacy and toxicity.

I discuss in more detail in items (a)-(b) below a number of reasons why a person skilled in the art, who read the Yue '566 specification in June 1999, would have concluded based on that specification and the state of the art at that time, that SEQ ID NO:12 polypeptide would be a highly useful tool for analysis of a 2-D PAGE map for evaluating the efficacy and toxicity of proposed drugs for cancer, immune disorders, neurological disorders, and gastrointestinal disorders by means of 2-D PAGE maps, as well as for other evaluations:

(a) The Yue '566 specification contains a number of teachings that would lead persons skilled in the art on June 16, 1999 to conclude that a 2-D PAGE map that utilized the substantially purified SEQ ID NO:12 polypeptide would be a more useful tool for protein expression monitoring applications relating to drugs for treating cancer, immune disorders, neurological disorders, and gastrointestinal disorders than a 2-D PAGE map that did not use the SEQ ID NO:12 polypeptide sequence. Among other things, the Yue '566 specification teaches that (i) the identity of the SEQ ID NO:12 polypeptide was determined from a "diseased gallbladder" tissue cDNA library (GBLANOT01) (Yue '566 application, Table 4), (ii) the SEQ ID NO:12 polypeptide is the annexin referred to as INSIG-12, and (iii) INSIG-12 is expressed in various libraries derived from reproductive, gastrointestinal, and nervous system tissues and in tissues associated with cancer and

inflammation (Yue '566 application at Table 3), and therefore "INSIG appears to play a role in cancer, immune disorders, neurological disorders, and gastrointestinal disorders" (Yue '566 application at p. 22; see paragraph 9, *supra*). The substantially purified polypeptide could therefore be used as a control to more accurately gauge the expression of INSIG in the sample and consequently more accurately gauge the affect of a toxicant on expression of the gene.

(b) Persons skilled in the art on June 16, 1999 would have appreciated (i) that the protein expression monitoring results obtained using a 2-D PAGE map that utilized a SEQ ID NO:12 polypeptide would vary, depending on the particular drug being evaluated, and (ii) that such varying results would occur both with respect to the results obtained from the SEQ ID NO:12 polypeptide and from the 2-D PAGE map as a whole (including all its other individual proteins). These kinds of varying results, depending on the identity of the drug being tested, in no way detracts from my conclusion that persons skilled in the art on June 16, 1999, having read the Yue '566 specification, would specifically request that any 2-D PAGE map that was being used for conducting protein expression monitoring studies on drugs for treating cancer, immune disorders, neurological disorders, and gastrointestinal disorders (*e.g.*, a toxicology study or any efficacy study of the type that typically takes place in connection with the development of a drug) utilize the SEQ ID NO:12 polypeptide sequence. Persons skilled in the art on June 16, 1999 would have wanted their 2-D PAGE map to utilize the SEQ ID NO:12 polypeptide sequence because a 2-D PAGE map that utilized protein sequence information the polypeptide (as compared to one that did not) would provide more useful results in the kind of protein expression monitoring studies using 2-D PAGE maps that persons skilled in the art have been doing since well prior to June 16, 1999.

The foregoing is not intended to be an all-inclusive explanation of all my reasons for reaching the conclusions stated in this paragraph 12, and in paragraph 6, *supra*. In my view, however, it provides more than sufficient reasons to justify my conclusions stated in paragraph 6 of this Declaration regarding the Yue '566 application disclosing to persons skilled in the art at the time of its filing substantial, specific and credible real-world utilities for the SEQ ID NO:12 polypeptide.

13. Also pertinent to my considerations underlying this Declaration is the fact that the Yue '566 disclosure regarding the uses of the SEQ ID NO:12 polypeptide for protein expression monitoring applications is not limited to the use of that protein in 2-D PAGE maps. For one thing, the Yue '566 disclosure regarding the technique used in gene and protein expression monitoring applications is broad (Yue '566 application at, e.g., p. 20, lines 16-20 and p. 31, lines 2-9).

In addition, the Yue '566 specification repeatedly teaches that the protein described therein (including the SEQ ID NO:12 polypeptide) may desirably be used in any of a number of long established "standard" techniques, such as ELISA or western blot analysis, for conducting protein expression monitoring studies. See, e.g.:

(a) Yue '566 application at p. 20, lines 21-24 ("Immunological methods for detecting and measuring the expression of INSIG using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS)");

(b) Yue '566 application at p. 31, lines 2-9 ("A variety of protocols for measuring INSIG, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of INSIG expression. Normal or standard values for INSIG expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, preferably human, with antibody to INSIG under conditions suitable for complex formation. The amount of standard complex formation may be quantitated by various methods, preferably by photometric means. Quantities of INSIG expressed in subject, control, and disease samples from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease").

Thus a person skilled in the art on June 16, 1999, who read the Yue '566 specification, would have routinely and readily appreciated that the SEQ ID NO:12 polypeptide disclosed therein would be useful to conduct protein expression monitoring analyses using 2-D PAGE mapping or western blot analysis or any of the other traditional membrane-based protein expression monitoring techniques that were known and in common use many years prior to the filing of the Yue '566 application. For example, a person skilled in the art in June 1999 would have routinely and readily

appreciated that the SEQ ID NO:12 polypeptide would be a useful tool in conducting protein expression analyses, using the 2-D PAGE mapping or western analysis techniques, in furtherance of (a) the development of drugs for the treatment of cancer, immune disorders, neurological disorders, and gastrointestinal disorders, and (b) analyses of the efficacy and toxicity of such drugs.

14. I declare further that all statements made herein of my own knowledge are true and that all statements made herein on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, and that willful false statements may jeopardize the validity of this application and any patent issuing thereon.



L. Michael Furness, B.Sc.

Signed at Exning, United Kingdom  
this 18<sup>th</sup> day of August, 2003

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: [Mail Stop: Non-Fee Amendment], Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on \_\_\_\_\_

August 27, 2003

By: Katherine Sofer

Printed: Katherine Sofer

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Yue et al.

Title: INTRACELLULAR SIGNALING MOLECULES

Serial No.: 10/018,170 Filing Date: December 11, 2001

Examiner: Steadman, D Group Art Unit: 1652

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Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

**DECLARATION OF LARS MICHAEL FURNESS**  
**UNDER 37 C.F.R. § 1.132**

I, L. MICHAEL FURNESS, a citizen of the United Kingdom, residing at 2 Brookside, Exning, Newmarket, United Kingdom, declare that:

1. I was employed by Incyte Genomics, Inc. (hereinafter "Incyte") as a Director of Pharmacogenomics until December 31, 2001. I am currently under contract to be a Consultant to Incyte Genomics, Inc.

2. In 1984, I received a B.Sc.(Hons) in Biomolecular Science (Biophysics and Biochemistry) from Portsmouth Polytechnic.

From 1985-1987 I was at the School of Pharmacy in London, United Kingdom, during which time I analyzed lipid methyltransferase enzymes using a variety of protein analysis methods, including one-dimensional (1D) and two-dimensional (2D) gel electrophoresis, HPLC, and a variety of enzymatic assay systems.

I then worked in the Protein Structure group at the National Institute for Medical Research until 1989, setting up core facilities for nucleic acid synthesis and sequencing, as well as assisting in programs on protein kinase C inhibitors.

After a year at Perkin Elmer-Applied Biosystems as a technical specialist, I worked at the Imperial Cancer Research Fund between 1990-1992, on a Eureka-funded program collaborating with Amersham Pharmacia in the United Kingdom and CEPH (Centre d'Etude du Polymorphisme Humaine) in Paris, France, to develop novel nucleic acid purification and characterization methods.

In 1992, I moved to Pfizer Central Research in the United Kingdom, where I stayed until 1998, initially setting up core DNA sequencing and then a DNA arraying facility for gene expression analysis in 1993. My work also included bioinformatics and I was responsible for the support of all Pfizer neuroscience programs in the United Kingdom. This then led me into carrying out detailed bioinformatics and wet lab work on the sodium channels, including antibody generation, Western and Northern analyses, PCR, tissue distribution studies, and sequence analyses on novel sequences identified.

In 1998, I moved to Incyte Genomics, Inc., to the Pharmacogenomics group to look at the application of genomics and proteomics to the pharmaceutical industry. In 1999, I was appointed director of the LifeExpress Lead Program which used microarray and protein expression data to identify pharmacologically and toxicologically relevant mechanisms to assist in improved drug design and development.

On December 12, 2001 I founded Nuomics Consulting Ltd., in Exning, U.K., and I am currently employed as Managing Director. Nuomics Consulting Ltd. will be providing expert technical knowledge and advice to businesses around the areas of genomics, proteomics, pharmacogenomics, toxicogenomics and chemogenomics.

3. I have reviewed the specification of a United States patent application that I understand was filed on December 11, 2001 in the names of Yue et al. and was assigned Serial No. 10/018,170 (hereinafter "the Yue '170 application"). Furthermore, I understand that this United States patent application claimed priority to United States Provisional Patent Application Serial No.

60/139,566 filed on June 16, 1999 (hereinafter "the Yue '566 application"). The SEQ ID NO:12-encoding polynucleotides were described in the Yue '566 application. (Note that the sequences of SEQ ID NO:12 and SEQ ID NO:64 disclosed in the Yue '170 application are identical to the sequences referred to as SEQ ID NO:12 and SEQ ID NO:31, respectively, in the Yue '566 application). My remarks herein will therefore be directed to the Yue '566 patent application, and June 16, 1999, as the relevant date of filing. In broad overview, the Yue '566 specification pertains to certain nucleotide and amino acid sequences and their use in a number of applications, including gene and protein expression monitoring applications that are useful in connection with (a) developing drugs (e.g., for the treatment of cancer), and (b) monitoring the activity of drugs for purposes relating to evaluating their efficacy and toxicity.

4. I understand that (a) the Yue '170 application contains claims that are directed to a substantially purified polypeptide having the sequence disclosed in the Yue '170 application as SEQ ID NO:12 (hereinafter "the SEQ ID NO:12 polypeptide"), and (b) the Patent Examiner has rejected those claims on the grounds that the specification of the Yue '170 application does not disclose a substantial, specific and credible utility for the claimed SEQ ID NO:12 polypeptide. I further understand that whether or not a patent specification discloses a substantial, specific and credible utility for its claimed subject matter is properly determined from the perspective of a person skilled in the art to which the specification pertains at the time of the patent application was filed. In addition, I understand that a substantial, specific and credible utility under the patent laws must be a "real-world" utility.

5. I have been asked (a) to consider with a view to reaching a conclusion (or conclusions) as to whether or not I agree with the Patent Examiner's position that the Yue '170 application and its parent, the Yue '566 application, does not disclose a substantial, specific and credible "real-world" utility for the claimed SEQ ID NO:12 polypeptide, and (b) to state and explain the bases for any conclusions I reach. I have been informed that, in connection with my considerations, I should determine whether or not a person skilled in the art to which the Yue '566 application pertains

on June 16, 1999, would have concluded that the '566 application disclosed, for the benefit of the public, a specific beneficial use of the SEQ ID NO:12 polypeptide in its then available and disclosed form. I have also been informed that, with respect to the "real-world" utility requirement, the Patent and Trademark Office instructs its Patent Examiners in Section 2107 of the Manual of Patent Examining Procedure, under the heading "I. 'Real-World Value' Requirement":

"Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact 'useful' in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified utility and inventions whose specific utility requires further research to identify or reasonably confirm."

6. I have considered the matters set forth in paragraph 5 of this Declaration and have concluded that, contrary to the position I understand the Patent Examiner has taken, the specification of the Yue '566 patent application disclosed to a person skilled in the art at the time of its filing a number of substantial, specific and credible real-world utilities for the claimed SEQ ID NO:12 polypeptide. More specifically, persons skilled in the art on June 16, 1999 would have understood the Yue '566 application to disclose the use of the SEQ ID NO:12 polypeptide as a research tool in a number of gene and protein expression monitoring applications that were well-known at that time to be useful in connection with the development of drugs and the monitoring of the activity of such drugs. I explain the bases for reaching my conclusion in this regard in paragraphs 7-13 below.

7. In reaching the conclusion stated in paragraph 6 of this Declaration, I considered (a) the specification of the Yue '566 application, and (b) a number of published articles and patent documents that evidence gene and protein expression monitoring techniques that were well-known before the June 16, 1999 filing date of the Yue '566 application. The published articles and patent documents I considered are:

(a) Anderson, N.L., Esquer-Blasco, R., Hofmann, J.-P., Anderson, N.G.,

A Two-Dimensional Gel Database of Rat Liver Proteins Useful in Gene Regulation and Drug Effects Studies, Electrophoresis, 12, 907-930 (1991) (hereinafter "the Anderson 1991 article") (copy annexed at Tab A);

(b) Anderson, N.L., Esquer-Blasco, R., Hofmann, J.-P., Mehues, L.,

Raymackers, J., Steiner, S., Witzmann, F., Anderson, N.G., An Updated Two-Dimensional Gel Database of Rat Liver Proteins Useful in Gene Regulation and Drug Effect Studies, Electrophoresis, 16, 1977-1981 (1995) (hereinafter "the Anderson 1995 article") (copy annexed at Tab B);

(c) Wilkins, M.R., Sanchez, J.-C., Gooley, A.A., Appel, R.D.,

Humphery-Smith, I., Hochstrasser, D.F., Williams, K.L., Progress with Proteome Projects: Why all Proteins Expressed by a Genome Should be Identified and How To Do It, Biotechnology and Genetic Engineering Reviews, 13, 19-50 (1995) (hereinafter "the Wilkins article") (copy annexed at Tab C);

(d) Celis, J.E., Rasmussen, H.H., Leffers, H., Madsen, P., Honore, B.,

Gesser, B., Dejgaard, K., Vandekerckhove, J., Human Cellular Protein Patterns and their Link to Genome DNA Sequence Data: Usefulness of Two-Dimensional Gel Electrophoresis and Microsequencing, FASEB Journal, 5, 2200-2208 (1991) (hereinafter "the Celis article") (copy annexed at Tab D);

(e) Franzen, B., Linder, S., Okuzawa, K., Kato, H., Auer, G.,

Nonenzymatic Extraction of Cells from Clinical Tumor Material for Analysis of Gene Expression by Two-Dimensional Polyacrylamide Gel Electrophoresis, Electrophoresis, 14, 1045-1053 (1993) (hereinafter "the Franzen article") (copy annexed at Tab E);

(f) Bjellqvist, B., Basse, B., Olsen, E., Celis, J.E., Reference Points for Comparisons of Two-Dimensional Maps of Proteins from Different Human Cell Types Defined in a pH Scale Where Isoelectric Points Correlate with Polypeptide Compositions, Electrophoresis, 15, 529-

539 (1994) (hereinafter "the Bjellqvist article") (copy annexed at Tab F);

(g) Large Scale Biology Company Info; LSB and LSP Information; from <http://www.lsbc.com> (2001) (copy annexed at Tab G);

8. Many of the published articles I considered (i.e., at least items (a)-(f) identified in paragraph 7) relate to the development of protein two-dimensional gel electrophoretic techniques for use in protein expression monitoring applications in drug development and toxicology. As I will discuss below, a person skilled in the art who read the Yue '566 application on June 16, 1999 would have understood that application to disclose the SEQ ID NO:12 polypeptide to be useful for a number of protein expression monitoring applications, e.g., in the use of two-dimensional polyacrylamide gel electrophoresis and western blot analysis of tissue samples in drug development and in toxicity testing.

Furthermore, items (a)-(f) establish that protein two-dimensional polyacrylamide gel electrophoresis and western blot analysis were well-known and established methods routinely used in toxicology testing and drug development at the time of filing the Yue '566 application and for several years prior to June 16, 1999. As such, one of ordinary skill in the art would have recognized that the polypeptide of SEQ ID NO:12 could be used in toxicology testing and drug development, irrespective of its biochemical activities.

9. Turning more specifically to the Yue '566 specification, the SEQ ID NO:12 polypeptide is shown at pages 14-15 as one of 38 sequences under the heading "Sequence Listing." The Yue '566 specification specifically teaches that the invention features a "substantially purified" polypeptide, human annexin (INSIG-12) having the amino acid sequence shown in SEQ ID NO:12" (Yue '566 application at p. 3 and Table 2). It further teaches that (a) the identity of the SEQ ID NO:12 polypeptide was determined from a diseased gallbladder tissue cDNA library (GBLANOT01) (Yue '566 application, Table 4), (b) the SEQ ID NO:12 polypeptide is the annexin referred to as "INSIG-12" and is encoded by SEQ ID NO:64, and (c) northern analysis shows that "INSIG-12 is expressed predominantly in cDNA libraries associated with reproductive, gastrointestinal, and nervous system tissues and in tissues associated with cancer and inflammation (Yue '566 application at Table 3).

The Yue '566 application discusses a number of uses of the SEQ ID NO:12 polypeptide in addition to its use in protein expression monitoring applications. I have not fully evaluated these additional uses in connection with the preparation of this Declaration and do not

express any views in this Declaration regarding whether or not the Yue '566 specification discloses these additional uses to be substantial, specific and credible real-world utilities of the SEQ ID NO:12 polypeptide. Consequently, my discussion in this Declaration concerning the Yue '566 application focuses on the portions of the application that relate to the use of the SEQ ID NO:12 polypeptide in gene and protein expression monitoring applications.

10. The Yue '566 application discloses that the polynucleotide sequences disclosed therein, including the polynucleotides encoding the SEQ ID NO:12 polypeptide, are useful as probes in chip based technologies. It further teaches that the chip based technologies can be used "for the detection and/or quantification of nucleic acid or protein" (Yue '566 application at p. 20, lines 17-20).

The Yue '566 application also discloses that the SEQ ID NO:12 polypeptide is useful in other protein expression detection technologies. The Yue '566 application states that "[a] methods for detecting and measuring the expression of INSIG using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS)" (Yue '566 application at p. 20, lines 21-24). Furthermore, the Yue '566 application discloses that "[a] variety of protocols for measuring INSIG, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of INSIG expression. Normal or standard values for INSIG expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, preferably human, with antibody to INSIG under conditions suitable for complex formation" (Yue '566 application at p. 31, lines 2-6).

In addition, at the time of filing the Yue '566 application, it was well known in the art that "gene" and protein expression analyses also included two-dimensional polyacrylamide gel electrophoresis (2-D PAGE) technologies, which were developed during the 1980s, and as exemplified by the Anderson 1991 and 1995 articles (Tab A and Tab B). The Anderson 1991 article teaches that a 2-D PAGE map has been used to connect and compare hundreds of 2-D gels of rat liver samples from a variety of studies including regulation of protein expression by various drugs and toxic agents (Tab A at p. 907). The Anderson 1991 article teaches an empirically-determined standard curve fitted

to a series of identified proteins based upon amino acid chain length (Tab A at p. 911) and how that standard curve can be used in protein expression analysis. The Anderson 1991 article teaches that "there is a long-term need for a comprehensive database of liver proteins" (Tab A at p. 912).

The Wilkins article is one of a number of documents that were published prior to the June 16, 1999 filing date of the Yue '566 application that describes the use of the 2-D PAGE technology in a wide range of gene and protein expression monitoring applications, including monitoring and analyzing protein expression patterns in human cancer, human serum plasma proteins, and in rodent liver following exposure to toxins. In view of the Yue '566 application, the Wilkins article, and other related pre-June 1999 publications, persons skilled in the art on June 16, 1999 clearly would have understood the Yue '566 application to disclose the SEQ ID NO:12 polypeptide to be useful in 2-D PAGE analyses for the development of new drugs and monitoring the activities of drugs for such purposes as evaluating their efficacy and toxicity, as explained more fully in paragraph 12 below.

With specific reference to toxicity evaluations, those of skill in the art who were working on drug development in June 1999 (and for many years prior to June 1999) without any doubt appreciated that the toxicity (or lack of toxicity) of any proposed drug they were working on was one of the most important criteria to be considered and evaluated in connection with the development of the drug. They would have understood at that time that good drugs are not only potent, they are specific. This means that they have strong effects on a specific biological target and minimal effects on all other biological targets. Ascertaining that a candidate drug affects its intended target, and identification of undesirable secondary effects (i.e., toxic side effects), had been for many years among the main challenges in developing new drugs. The ability to determine which genes are positively affected by a given drug, coupled with the ability to quickly and at the earliest time possible in the drug development process identify drugs that are likely to be toxic because of their undesirable secondary effects, have enormous value in improving the efficiency of the drug discovery process, and are an important and essential part of the development of any new drug. In fact, the desire to identify and understand toxicological effects using the experimental assays described above led Dr Leigh Anderson to found the Large Scale Biology Corporation in 1985, in order to pursue commercial development of the 2-D electrophoretic protein mapping technology he had developed. In addition, the company focused on

toxicological effects on the proteome as clearly demonstrated by its goals and by its senior management credentials described in company documents (see Tab G at pp. 1, 3, and 5).

Accordingly, the teachings in the Yue '566 application, in particular regarding use of SEQ ID NO:12 in differential gene and protein expression analysis (2-D PAGE maps) and in the development and the monitoring of the activities of drugs, clearly includes toxicity studies and persons skilled in the art who read the Yue '566 application on June 16, 1999 would have understood that to be so.

11. As previously discussed (*supra*, paragraphs 7 and 8), my experience with protein analysis methods in the mid-1980s and the several publications annexed to this Declaration at Tabs A through F evidence information that was available to the public regarding two-dimensional polyacrylamide gel electrophoresis technology and its uses in drug discovery and toxicology testing before the June 16, 1999 filing date of the Yue '566 application. In particular the Celis article stated that "protein databases are expected to foster a variety of biological information.... -- among others, .... drug development and testing" (See Tab D, p. 2200, second column). The Franzen article shows that 2-D PAGE maps were used to identify proteins in clinical tumor material (See Tab E). The Yue '566 application clearly discloses that expression of IINSIG is associated with reproductive, gastrointestinal, and nervous system tissues and tissues associated with cancer and inflammation. (Yue '566 application at Table 3). The Bjellqvist article showed that a protein may be identified accurately by its positional co-ordinates, namely molecular mass and isoelectric point (See Tab F). The Yue '566 application clearly disclosed SEQ ID NO:12 from which it would have been routine for one of skill in the art to predict both the molecular mass and the isoelectric point using algorithms well known in the art at the time of filing.

12. A person skilled in the art on June 16, 1999, who read the Yue '566 application, would understand that application to disclose the SEQ ID NO:12 polypeptide to be highly useful in analysis of differential expression of proteins. For example, the specification of the Yue '566 application would have led a person skilled in the art in June 1999 who was using protein expression

monitoring in connection with working on developing new drugs for the treatment of an cancer, immune disorders, neurological disorders, and gastrointestinal disorders to conclude that a 2-D PAGE map that used the substantially purified SEQ ID NO:12 polypeptide would be a highly useful tool and to request specifically that any 2-D PAGE map that was being used for such purposes utilize the SEQ ID NO:12 polypeptide sequence. Expressed proteins are useful for 2-D PAGE analysis in toxicology expression studies for a variety of reasons, particularly for purposes relating to providing controls for the 2-D PAGE analysis, and for identifying sequence or post-translational variants of the expressed sequences in response to exogenous compounds. Persons skilled in the art would appreciate that a 2-D PAGE map that utilized the SEQ ID NO:12 polypeptide sequence would be a more useful tool than a 2-D PAGE map that did not utilize this protein sequence in connection with conducting protein expression monitoring studies on proposed (or actual) drugs for treating cancer, immune disorders, neurological disorders, and gastrointestinal disorders for such purposes as evaluating their efficacy and toxicity.

I discuss in more detail in items (a)-(b) below a number of reasons why a person skilled in the art, who read the Yue '566 specification in June 1999, would have concluded based on that specification and the state of the art at that time, that SEQ ID NO:12 polypeptide would be a highly useful tool for analysis of a 2-D PAGE map for evaluating the efficacy and toxicity of proposed drugs for cancer, immune disorders, neurological disorders, and gastrointestinal disorders by means of 2-D PAGE maps, as well as for other evaluations:

(a) The Yue '566 specification contains a number of teachings that would lead persons skilled in the art on June 16, 1999 to conclude that a 2-D PAGE map that utilized the substantially purified SEQ ID NO:12 polypeptide would be a more useful tool for protein expression monitoring applications relating to drugs for treating cancer, immune disorders, neurological disorders, and gastrointestinal disorders than a 2-D PAGE map that did not use the SEQ ID NO:12 polypeptide sequence. Among other things, the Yue '566 specification teaches that (i) the identity of the SEQ ID NO:12 polypeptide was determined from a "diseased gallbladder" tissue cDNA library (GBLANOT01) (Yue '566 application, Table 4), (ii) the SEQ ID NO:12 polypeptide is the annexin referred to as INSIG-12, and (iii) INSIG-12 is expressed in various libraries derived from reproductive, gastrointestinal, and nervous system tissues and in tissues associated with cancer and

inflammation (Yue '566 application at Table 3), and therefore "INSIG appears to play a role in cancer, immune disorders, neurological disorders, and gastrointestinal disorders" (Yue '566 application at p. 22; see paragraph 9, *supra*). The substantially purified polypeptide could therefore be used as a control to more accurately gauge the expression of INSIG in the sample and consequently more accurately gauge the affect of a toxicant on expression of the gene.

(b) Persons skilled in the art on June 16, 1999 would have appreciated (i) that the protein expression monitoring results obtained using a 2-D PAGE map that utilized a SEQ ID NO:12 polypeptide would vary, depending on the particular drug being evaluated, and (ii) that such varying results would occur both with respect to the results obtained from the SEQ ID NO:12 polypeptide and from the 2-D PAGE map as a whole (including all its other individual proteins). These kinds of varying results, depending on the identity of the drug being tested, in no way detracts from my conclusion that persons skilled in the art on June 16, 1999, having read the Yue '566 specification, would specifically request that any 2-D PAGE map that was being used for conducting protein expression monitoring studies on drugs for treating cancer, immune disorders, neurological disorders, and gastrointestinal disorders (*e.g.*, a toxicology study or any efficacy study of the type that typically takes place in connection with the development of a drug) utilize the SEQ ID NO:12 polypeptide sequence. Persons skilled in the art on June 16, 1999 would have wanted their 2-D PAGE map to utilize the SEQ ID NO:12 polypeptide sequence because a 2-D PAGE map that utilized protein sequence information the polypeptide (as compared to one that did not) would provide more useful results in the kind of protein expression monitoring studies using 2-D PAGE maps that persons skilled in the art have been doing since well prior to June 16, 1999.

The foregoing is not intended to be an all-inclusive explanation of all my reasons for reaching the conclusions stated in this paragraph 12, and in paragraph 6, *supra*. In my view, however, it provides more than sufficient reasons to justify my conclusions stated in paragraph 6 of this Declaration regarding the Yue '566 application disclosing to persons skilled in the art at the time of its filing substantial, specific and credible real-world utilities for the SEQ ID NO:12 polypeptide.

13. Also pertinent to my considerations underlying this Declaration is the fact that the Yue '566 disclosure regarding the uses of the SEQ ID NO:12 polypeptide for protein expression monitoring applications is not limited to the use of that protein in 2-D PAGE maps. For one thing, the Yue '566 disclosure regarding the technique used in gene and protein expression monitoring applications is broad (Yue '566 application at, e.g., p. 20, lines 16-20 and p. 31, lines 2-9).

In addition, the Yue '566 specification repeatedly teaches that the protein described therein (including the SEQ ID NO:12 polypeptide) may desirably be used in any of a number of long established "standard" techniques, such as ELISA or western blot analysis, for conducting protein expression monitoring studies. See, e.g.:

(a) Yue '566 application at p. 20, lines 21-24 ("Immunological methods for detecting and measuring the expression of INSIG using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS)");

(b) Yue '566 application at p. 31, lines 2-9 ("A variety of protocols for measuring INSIG, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of INSIG expression. Normal or standard values for INSIG expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, preferably human, with antibody to INSIG under conditions suitable for complex formation. The amount of standard complex formation may be quantitated by various methods, preferably by photometric means. Quantities of INSIG expressed in subject, control, and disease samples from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease").

Thus a person skilled in the art on June 16, 1999, who read the Yue '566 specification, would have routinely and readily appreciated that the SEQ ID NO:12 polypeptide disclosed therein would be useful to conduct protein expression monitoring analyses using 2-D PAGE mapping or western blot analysis or any of the other traditional membrane-based protein expression monitoring techniques that were known and in common use many years prior to the filing of the Yue '566 application. For example, a person skilled in the art in June 1999 would have routinely and readily

appreciated that the SEQ ID NO:12 polypeptide would be a useful tool in conducting protein expression analyses, using the 2-D PAGE mapping or western analysis techniques, in furtherance of (a) the development of drugs for the treatment of cancer, immune disorders, neurological disorders, and gastrointestinal disorders, and (b) analyses of the efficacy and toxicity of such drugs.

14. I declare further that all statements made herein of my own knowledge are true and that all statements made herein on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, and that willful false statements may jeopardize the validity of this application and any patent issuing thereon.



L. Michael Furness, B.Sc.

Signed at Exning, United Kingdom

this 18<sup>th</sup> day of August, 2003

Certificate of Mailing

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: [Mail Stop: Non-Fee Amendment], Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on \_\_\_\_\_

August 27, 2003

By: Katherine Sofer

Printed: Katherine Sofer

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of: Yue et al.

Title: INTRACELLULAR SIGNALING MOLECULES

Serial No.: 10/018,170 Filing Date: December 11, 2001

Examiner: Steadman, D Group Art Unit: 1652

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Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

**DECLARATION OF LARS MICHAEL FURNESS**  
**UNDER 37 C.F.R. § 1.132**

I, L. MICHAEL FURNESS, a citizen of the United Kingdom, residing at 2 Brookside, Exning, Newmarket, United Kingdom, declare that:

1. I was employed by Incyte Genomics, Inc. (hereinafter "Incyte") as a Director of Pharmacogenomics until December 31, 2001. I am currently under contract to be a Consultant to Incyte Genomics, Inc.

2. In 1984, I received a B.Sc.(Hons) in Biomolecular Science (Biophysics and Biochemistry) from Portsmouth Polytechnic.

From 1985-1987 I was at the School of Pharmacy in London, United Kingdom, during which time I analyzed lipid methyltransferase enzymes using a variety of protein analysis methods, including one-dimensional (1D) and two-dimensional (2D) gel electrophoresis, HPLC, and a variety of enzymatic assay systems.

I then worked in the Protein Structure group at the National Institute for Medical Research until 1989, setting up core facilities for nucleic acid synthesis and sequencing, as well as assisting in programs on protein kinase C inhibitors.

After a year at Perkin Elmer-Applied Biosystems as a technical specialist, I worked at the Imperial Cancer Research Fund between 1990-1992, on a Eureka-funded program collaborating with Amersham Pharmacia in the United Kingdom and CEPH (Centre d'Etude du Polymorphisme Humaine) in Paris, France, to develop novel nucleic acid purification and characterization methods.

In 1992, I moved to Pfizer Central Research in the United Kingdom, where I stayed until 1998, initially setting up core DNA sequencing and then a DNA arraying facility for gene expression analysis in 1993. My work also included bioinformatics and I was responsible for the support of all Pfizer neuroscience programs in the United Kingdom. This then led me into carrying out detailed bioinformatics and wet lab work on the sodium channels, including antibody generation, Western and Northern analyses, PCR, tissue distribution studies, and sequence analyses on novel sequences identified.

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On December 12, 2001 I founded Nuomics Consulting Ltd., in Exning, U.K., and I am currently employed as Managing Director. Nuomics Consulting Ltd. will be providing expert technical knowledge and advice to businesses around the areas of genomics, proteomics, pharmacogenomics, toxicogenomics and chemogenomics.

3. I have reviewed the specification of a United States patent application that I understand was filed on December 11, 2001 in the names of Yue et al. and was assigned Serial No. 10/018,170 (hereinafter "the Yue '170 application"). Furthermore, I understand that this United States patent application claimed priority to United States Provisional Patent Application Serial No.

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4. I understand that (a) the Yue '170 application contains claims that are directed to a substantially purified polypeptide having the sequence disclosed in the Yue '170 application as SEQ ID NO:12 (hereinafter "the SEQ ID NO:12 polypeptide"), and (b) the Patent Examiner has rejected those claims on the grounds that the specification of the Yue '170 application does not disclose a substantial, specific and credible utility for the claimed SEQ ID NO:12 polypeptide. I further understand that whether or not a patent specification discloses a substantial, specific and credible utility for its claimed subject matter is properly determined from the perspective of a person skilled in the art to which the specification pertains at the time of the patent application was filed. In addition, I understand that a substantial, specific and credible utility under the patent laws must be a "real-world" utility.

5. I have been asked (a) to consider with a view to reaching a conclusion (or conclusions) as to whether or not I agree with the Patent Examiner's position that the Yue '170 application and its parent, the Yue '566 application, does not disclose a substantial, specific and credible "real-world" utility for the claimed SEQ ID NO:12 polypeptide, and (b) to state and explain the bases for any conclusions I reach. I have been informed that, in connection with my considerations, I should determine whether or not a person skilled in the art to which the Yue '566 application pertains

on June 16, 1999, would have concluded that the '566 application disclosed, for the benefit of the public, a specific beneficial use of the SEQ ID NO:12 polypeptide in its then available and disclosed form. I have also been informed that, with respect to the "real-world" utility requirement, the Patent and Trademark Office instructs its Patent Examiners in Section 2107 of the Manual of Patent Examining Procedure, under the heading "I. 'Real-World Value' Requirement":

"Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact 'useful' in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified utility and inventions whose specific utility requires further research to identify or reasonably confirm."

6. I have considered the matters set forth in paragraph 5 of this Declaration and have concluded that, contrary to the position I understand the Patent Examiner has taken, the specification of the Yue '566 patent application disclosed to a person skilled in the art at the time of its filing a number of substantial, specific and credible real-world utilities for the claimed SEQ ID NO:12 polypeptide. More specifically, persons skilled in the art on June 16, 1999 would have understood the Yue '566 application to disclose the use of the SEQ ID NO:12 polypeptide as a research tool in a number of gene and protein expression monitoring applications that were well-known at that time to be useful in connection with the development of drugs and the monitoring of the activity of such drugs. I explain the bases for reaching my conclusion in this regard in paragraphs 7-13 below.

7. In reaching the conclusion stated in paragraph 6 of this Declaration, I considered (a) the specification of the Yue '566 application, and (b) a number of published articles and patent documents that evidence gene and protein expression monitoring techniques that were well-known before the June 16, 1999 filing date of the Yue '566 application. The published articles and patent documents I considered are:

(a) Anderson, N.L., Esquer-Blasco, R., Hofmann, J.-P., Anderson, N.G., A Two-Dimensional Gel Database of Rat Liver Proteins Useful in Gene Regulation and Drug Effects Studies, Electrophoresis, 12, 907-930 (1991) (hereinafter "the Anderson 1991 article") (copy annexed at Tab A);

(b) Anderson, N.L., Esquer-Blasco, R., Hofmann, J.-P., Mehues, L., Raymackers, J., Steiner, S. Witzmann, F., Anderson, N.G., An Updated Two-Dimensional Gel Database of Rat Liver Proteins Useful in Gene Regulation and Drug Effect Studies, Electrophoresis, 16, 1977-1981 (1995) (hereinafter "the Anderson 1995 article") (copy annexed at Tab B);

(c) Wilkins, M.R., Sanchez, J.-C., Gooley, A.A., Appel, R.D., Humphery-Smith, I., Hochstrasser, D.F., Williams, K.L., Progress with Proteome Projects: Why all Proteins Expressed by a Genome Should be Identified and How To Do It, Biotechnology and Genetic Engineering Reviews, 13, 19-50 (1995) (hereinafter "the Wilkins article") (copy annexed at Tab C);

(d) Celis, J.E., Rasmussen, H.H., Leffers, H., Madsen, P., Honore, B., Gesser, B., Dejgaard, K., Vandekerckhove, J., Human Cellular Protein Patterns and their Link to Genome DNA Sequence Data: Usefulness of Two-Dimensional Gel Electrophoresis and Microsequencing, FASEB Journal, 5, 2200-2208 (1991) (hereinafter "the Celis article") (copy annexed at Tab D);

(e) Franzen, B., Linder, S., Okuzawa, K., Kato, H., Auer, G., Nonenzymatic Extraction of Cells from Clinical Tumor Material for Analysis of Gene Expression by Two-Dimensional Polyacrylamide Gel Electrophoresis, Electrophoresis, 14, 1045-1053 (1993) (hereinafter "the Franzen article") (copy annexed at Tab E);

(f) Bjellqvist, B., Basse, B., Olsen, E., Celis, J.E., Reference Points for Comparisons of Two-Dimensional Maps of Proteins from Different Human Cell Types Defined in a pH Scale Where Isoelectric Points Correlate with Polypeptide Compositions, Electrophoresis, 15, 529-539 (1994) (hereinafter "the Bjellqvist article") (copy annexed at Tab F);

(g) Large Scale Biology Company Info; LSB and LSP Information; from <http://www.lsbc.com> (2001) (copy annexed at Tab G);

8. Many of the published articles I considered (i.e., at least items (a)-(f) identified in paragraph 7) relate to the development of protein two-dimensional gel electrophoretic techniques for use in protein expression monitoring applications in drug development and toxicology. As I will discuss below, a person skilled in the art who read the Yue '566 application on June 16, 1999 would have understood that application to disclose the SEQ ID NO:12 polypeptide to be useful for a number of protein expression monitoring applications, e.g., in the use of two-dimensional polyacrylamide gel electrophoresis and western blot analysis of tissue samples in drug development and in toxicity testing.

Furthermore, items (a)-(f) establish that protein two-dimensional polyacrylamide gel electrophoresis and western blot analysis were well-known and established methods routinely used in toxicology testing and drug development at the time of filing the Yue '566 application and for several years prior to June 16, 1999. As such, one of ordinary skill in the art would have recognized that the polypeptide of SEQ ID NO:12 could be used in toxicology testing and drug development, irrespective of its biochemical activities.

9. Turning more specifically to the Yue '566 specification, the SEQ ID NO:12 polypeptide is shown at pages 14-15 as one of 38 sequences under the heading "Sequence Listing." The Yue '566 specification specifically teaches that the invention features a "substantially purified" polypeptide, human annexin (INSIG-12) having the amino acid sequence shown in SEQ ID NO:12" (Yue '566 application at p. 3 and Table 2). It further teaches that (a) the identity of the SEQ ID NO:12 polypeptide was determined from a diseased gallbladder tissue cDNA library (GBLANOT01) (Yue '566 application, Table 4), (b) the SEQ ID NO:12 polypeptide is the annexin referred to as "INSIG-12" and is encoded by SEQ ID NO:64, and (c) northern analysis shows that "INSIG-12 is expressed predominantly in cDNA libraries associated with reproductive, gastrointestinal, and nervous system tissues and in tissues associated with cancer and inflammation (Yue '566 application at Table 3).

The Yue '566 application discusses a number of uses of the SEQ ID NO:12 polypeptide in addition to its use in protein expression monitoring applications. I have not fully evaluated these additional uses in connection with the preparation of this Declaration and do not

express any views in this Declaration regarding whether or not the Yue '566 specification discloses these additional uses to be substantial, specific and credible real-world utilities of the SEQ ID NO:12 polypeptide. Consequently, my discussion in this Declaration concerning the Yue '566 application focuses on the portions of the application that relate to the use of the SEQ ID NO:12 polypeptide in gene and protein expression monitoring applications.

10. The Yue '566 application discloses that the polynucleotide sequences disclosed therein, including the polynucleotides encoding the SEQ ID NO:12 polypeptide, are useful as probes in chip based technologies. It further teaches that the chip based technologies can be used "for the detection and/or quantification of nucleic acid or protein" (Yue '566 application at p. 20, lines 17-20).

The Yue '566 application also discloses that the SEQ ID NO:12 polypeptide is useful in other protein expression detection technologies. The Yue '566 application states that "[a] methods for detecting and measuring the expression of INSIG using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS)" (Yue '566 application at p. 20, lines 21-24). Furthermore, the Yue '566 application discloses that "[a] variety of protocols for measuring INSIG, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of INSIG expression. Normal or standard values for INSIG expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, preferably human, with antibody to INSIG under conditions suitable for complex formation" (Yue '566 application at p. 31, lines 2-6).

In addition, at the time of filing the Yue '566 application, it was well known in the art that "gene" and protein expression analyses also included two-dimensional polyacrylamide gel electrophoresis (2-D PAGE) technologies, which were developed during the 1980s, and as exemplified by the Anderson 1991 and 1995 articles (Tab A and Tab B). The Anderson 1991 article teaches that a 2-D PAGE map has been used to connect and compare hundreds of 2-D gels of rat liver samples from a variety of studies including regulation of protein expression by various drugs and toxic agents (Tab A at p. 907). The Anderson 1991 article teaches an empirically-determined standard curve fitted

to a series of identified proteins based upon amino acid chain length (Tab A at p. 911) and how that standard curve can be used in protein expression analysis. The Anderson 1991 article teaches that "there is a long-term need for a comprehensive database of liver proteins" (Tab A at p. 912).

The Wilkins article is one of a number of documents that were published prior to the June 16, 1999 filing date of the Yue '566 application that describes the use of the 2-D PAGE technology in a wide range of gene and protein expression monitoring applications, including monitoring and analyzing protein expression patterns in human cancer, human serum plasma proteins, and in rodent liver following exposure to toxins. In view of the Yue '566 application, the Wilkins article, and other related pre-June 1999 publications, persons skilled in the art on June 16, 1999 clearly would have understood the Yue '566 application to disclose the SEQ ID NO:12 polypeptide to be useful in 2-D PAGE analyses for the development of new drugs and monitoring the activities of drugs for such purposes as evaluating their efficacy and toxicity, as explained more fully in paragraph 12 below.

With specific reference to toxicity evaluations, those of skill in the art who were working on drug development in June 1999 (and for many years prior to June 1999) without any doubt appreciated that the toxicity (or lack of toxicity) of any proposed drug they were working on was one of the most important criteria to be considered and evaluated in connection with the development of the drug. They would have understood at that time that good drugs are not only potent, they are specific. This means that they have strong effects on a specific biological target and minimal effects on all other biological targets. Ascertaining that a candidate drug affects its intended target, and identification of undesirable secondary effects (i.e., toxic side effects), had been for many years among the main challenges in developing new drugs. The ability to determine which genes are positively affected by a given drug, coupled with the ability to quickly and at the earliest time possible in the drug development process identify drugs that are likely to be toxic because of their undesirable secondary effects, have enormous value in improving the efficiency of the drug discovery process, and are an important and essential part of the development of any new drug. In fact, the desire to identify and understand toxicological effects using the experimental assays described above led Dr Leigh Anderson to found the Large Scale Biology Corporation in 1985, in order to pursue commercial development of the 2-D electrophoretic protein mapping technology he had developed. In addition, the company focused on

toxicological effects on the proteome as clearly demonstrated by its goals and by its senior management credentials described in company documents (see Tab G at pp. 1, 3, and 5).

Accordingly, the teachings in the Yue '566 application, in particular regarding use of SEQ ID NO:12 in differential gene and protein expression analysis (2-D PAGE maps) and in the development and the monitoring of the activities of drugs, clearly includes toxicity studies and persons skilled in the art who read the Yue '566 application on June 16, 1999 would have understood that to be so.

11. As previously discussed (*supra*, paragraphs 7 and 8), my experience with protein analysis methods in the mid-1980s and the several publications annexed to this Declaration at Tabs A through F evidence information that was available to the public regarding two-dimensional polyacrylamide gel electrophoresis technology and its uses in drug discovery and toxicology testing before the June 16, 1999 filing date of the Yue '566 application. In particular the Celis article stated that "protein databases are expected to foster a variety of biological information.... -- among others, .... drug development and testing" (See Tab D, p. 2200, second column). The Franzen article shows that 2-D PAGE maps were used to identify proteins in clinical tumor material (See Tab E). The Yue '566 application clearly discloses that expression of IINSIG is associated with reproductive, gastrointestinal, and nervous system tissues and tissues associated with cancer and inflammation. (Yue '566 application at Table 3). The Bjellqvist article showed that a protein may be identified accurately by its positional co-ordinates, namely molecular mass and isoelectric point (See Tab F). The Yue '566 application clearly disclosed SEQ ID NO:12 from which it would have been routine for one of skill in the art to predict both the molecular mass and the isoelectric point using algorithms well known in the art at the time of filing.

12. A person skilled in the art on June 16, 1999, who read the Yue '566 application, would understand that application to disclose the SEQ ID NO:12 polypeptide to be highly useful in analysis of differential expression of proteins. For example, the specification of the Yue '566 application would have led a person skilled in the art in June 1999 who was using protein expression

monitoring in connection with working on developing new drugs for the treatment of cancer, immune disorders, neurological disorders, and gastrointestinal disorders to conclude that a 2-D PAGE map that used the substantially purified SEQ ID NO:12 polypeptide would be a highly useful tool and to request specifically that any 2-D PAGE map that was being used for such purposes utilize the SEQ ID NO:12 polypeptide sequence. Expressed proteins are useful for 2-D PAGE analysis in toxicology expression studies for a variety of reasons, particularly for purposes relating to providing controls for the 2-D PAGE analysis, and for identifying sequence or post-translational variants of the expressed sequences in response to exogenous compounds. Persons skilled in the art would appreciate that a 2-D PAGE map that utilized the SEQ ID NO:12 polypeptide sequence would be a more useful tool than a 2-D PAGE map that did not utilize this protein sequence in connection with conducting protein expression monitoring studies on proposed (or actual) drugs for treating cancer, immune disorders, neurological disorders, and gastrointestinal disorders for such purposes as evaluating their efficacy and toxicity.

I discuss in more detail in items (a)-(b) below a number of reasons why a person skilled in the art, who read the Yue '566 specification in June 1999, would have concluded based on that specification and the state of the art at that time, that SEQ ID NO:12 polypeptide would be a highly useful tool for analysis of a 2-D PAGE map for evaluating the efficacy and toxicity of proposed drugs for cancer, immune disorders, neurological disorders, and gastrointestinal disorders by means of 2-D PAGE maps, as well as for other evaluations:

(a) The Yue '566 specification contains a number of teachings that would lead persons skilled in the art on June 16, 1999 to conclude that a 2-D PAGE map that utilized the substantially purified SEQ ID NO:12 polypeptide would be a more useful tool for protein expression monitoring applications relating to drugs for treating cancer, immune disorders, neurological disorders, and gastrointestinal disorders than a 2-D PAGE map that did not use the SEQ ID NO:12 polypeptide sequence. Among other things, the Yue '566 specification teaches that (i) the identity of the SEQ ID NO:12 polypeptide was determined from a "diseased gallbladder" tissue cDNA library (GBLANOT01) (Yue '566 application, Table 4), (ii) the SEQ ID NO:12 polypeptide is the annexin referred to as INSIG-12, and (iii) INSIG-12 is expressed in various libraries derived from reproductive, gastrointestinal, and nervous system tissues and in tissues associated with cancer and

inflammation (Yue '566 application at Table 3), and therefore "INSIG appears to play a role in cancer, immune disorders, neurological disorders, and gastrointestinal disorders" (Yue '566 application at p. 22; see paragraph 9, *supra*). The substantially purified polypeptide could therefore be used as a control to more accurately gauge the expression of INSIG in the sample and consequently more accurately gauge the affect of a toxicant on expression of the gene.

(b) Persons skilled in the art on June 16, 1999 would have appreciated (i) that the protein expression monitoring results obtained using a 2-D PAGE map that utilized a SEQ ID NO:12 polypeptide would vary, depending on the particular drug being evaluated, and (ii) that such varying results would occur both with respect to the results obtained from the SEQ ID NO:12 polypeptide and from the 2-D PAGE map as a whole (including all its other individual proteins). These kinds of varying results, depending on the identity of the drug being tested, in no way detracts from my conclusion that persons skilled in the art on June 16, 1999, having read the Yue '566 specification, would specifically request that any 2-D PAGE map that was being used for conducting protein expression monitoring studies on drugs for treating cancer, immune disorders, neurological disorders, and gastrointestinal disorders (*e.g.*, a toxicology study or any efficacy study of the type that typically takes place in connection with the development of a drug) utilize the SEQ ID NO:12 polypeptide sequence. Persons skilled in the art on June 16, 1999 would have wanted their 2-D PAGE map to utilize the SEQ ID NO:12 polypeptide sequence because a 2-D PAGE map that utilized protein sequence information the polypeptide (as compared to one that did not) would provide more useful results in the kind of protein expression monitoring studies using 2-D PAGE maps that persons skilled in the art have been doing since well prior to June 16, 1999.

The foregoing is not intended to be an all-inclusive explanation of all my reasons for reaching the conclusions stated in this paragraph 12, and in paragraph 6, *supra*. In my view, however, it provides more than sufficient reasons to justify my conclusions stated in paragraph 6 of this Declaration regarding the Yue '566 application disclosing to persons skilled in the art at the time of its filing substantial, specific and credible real-world utilities for the SEQ ID NO:12 polypeptide.

13. Also pertinent to my considerations underlying this Declaration is the fact that the Yue '566 disclosure regarding the uses of the SEQ ID NO:12 polypeptide for protein expression monitoring applications is not limited to the use of that protein in 2-D PAGE maps. For one thing, the Yue '566 disclosure regarding the technique used in gene and protein expression monitoring applications is broad (Yue '566 application at, e.g., p. 20, lines 16-20 and p. 31, lines 2-9).

In addition, the Yue '566 specification repeatedly teaches that the protein described therein (including the SEQ ID NO:12 polypeptide) may desirably be used in any of a number of long established "standard" techniques, such as ELISA or western blot analysis, for conducting protein expression monitoring studies. See, e.g.:

(a) Yue '566 application at p. 20, lines 21-24 ("Immunological methods for detecting and measuring the expression of INSIG using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS)").

(b) Yue '566 application at p. 31, lines 2-9 ("A variety of protocols for measuring INSIG, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of INSIG expression. Normal or standard values for INSIG expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, preferably human, with antibody to INSIG under conditions suitable for complex formation. The amount of standard complex formation may be quantitated by various methods, preferably by photometric means. Quantities of INSIG expressed in subject, control, and disease samples from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease").

Thus a person skilled in the art on June 16, 1999, who read the Yue '566 specification, would have routinely and readily appreciated that the SEQ ID NO:12 polypeptide disclosed therein would be useful to conduct protein expression monitoring analyses using 2-D PAGE mapping or western blot analysis or any of the other traditional membrane-based protein expression monitoring techniques that were known and in common use many years prior to the filing of the Yue '566 application. For example, a person skilled in the art in June 1999 would have routinely and readily

appreciated that the SEQ ID NO:12 polypeptide would be a useful tool in conducting protein expression analyses, using the 2-D PAGE mapping or western analysis techniques, in furtherance of (a) the development of drugs for the treatment of cancer, immune disorders, neurological disorders, and gastrointestinal disorders, and (b) analyses of the efficacy and toxicity of such drugs.

14. I declare further that all statements made herein of my own knowledge are true and that all statements made herein on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, and that willful false statements may jeopardize the validity of this application and any patent issuing thereon.



L. Michael Furness, B.Sc.

Signed at Exning, United Kingdom  
this 18<sup>th</sup> day of August, 2003

